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CONFERENCE ON GASTRIC CANCER

A conference on gastric cancer, sponsored by the National Advisory Cancer Council, United States Public Health Service, was held in Billings Hospital, University of Chicago, December 5–6, 1946.

THURSDAY MORNING SESSION

DECEMBER 5, 1946

The first session of the Gastric Cancer Conference convened at 9:30 a. m., Dr. Alexander Brunschwig, of the University of Chicago, presiding.

Chairman Brunschwig: Dr. Parran, Ladies, and Gentlemen: On behalf of the University I want to welcome you to the third Gastric Cancer Conference, which is being held under the auspices of the National Advisory Cancer Council, of the United States Public Health Service. The attendance here and the program testify to the rapidly increasing interest in pressing the attack upon gastric cancer, which, as you all know, is one of the most fatal forms of neoplastic disease.

It is with profound regret that we announce the absence of Dr. George M. Smith, of Yale University, Executive Director of the National Advisory Cancer Council. This conference is very close to his heart, and its success will be due in large measure to his untiring efforts.

It is a great privilege for us to have Surgeon General Parran, of the United States Public Health Service, open this conference. He is with us today because of his deep interest in the cancer problem. Dr. Parran.

A NATIONAL CANCER POLICY[1]

By THOMAS PARRAN, M. D., *Surgeon General, United States Public Health Service*

It is hardly necessary for me to point out to members of this conference that during the past few years cancer has emerged as one of the most urgent of our public health problems. Any disease that takes an annual toll of 175,000 persons must be of major concern to research workers, to public health officials, and above all to the American people, who suffer and die from it.

Although 30 years ago cancer stood seventh in the list of causes of death, today it ranks second. Unless we acquire greater mastery over this disease than we now have, through intensified research and more widespread application of facts already known, cancer will kill 20,000,000 Americans now living.

About 45 percent of all cancer deaths are caused by cancer of the digestive system. Gastric cancer alone accounts for 15 percent of the total cancer deaths. During World War II, the American armed forces lost about 300,000 men as a result of enemy action. During the same 4-year period, 1942 through 1945, the same number of Americans died of cancer of the digestive system. Thus it is evident that if your conference this week is successful, it will point the way to longer life for many of our fellow citizens.

The person who deserves the major credit for mobilizing the diverse group of experts assembled here today is Dr. George M. Smith. As a member of the National Advisory Cancer Council and later as its Executive Director, he has continued over the years to urge intensified research and correlation of the several disciplines needed to advance our knowledge of gastric cancer. In Dr. Smith's absence, may I express my own appreciation and his in welcoming you and in thanking each of you for contributing to the success of this conference, both through your previous work and your presence here.

Our previous conferences, at Bethesda in 1940 and at New York in 1944, aroused a great deal of interest among scientists concerned with gastric cancer and were influential in encouraging a number of new researches. Let us hope that the

[1] Address given at the Gastric Cancer Conference, Billings Hospital, Chicago, December 5, 1946.

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present conference will propose new methods of attack on gastric cancer and relate those efforts to the over-all problem posed by cancer. Concerted action by and interchange of information between groups such as this represent long steps toward the common goal of bringing cancer under control.

For the United States Public Health Service, I can report that two and one-half million dollars of grant-in-aid funds from the appropriation for general health are available this year for the first time to the State health agencies for work in cancer control. These funds will help provide more and better education about cancer, both for professional persons and the general public. They will help supply such facilities as cancer-detection clinics, and laboratory service for tissue diagnosis and will promote competent cancer-treatment centers. In short, these funds will be used better to apply the knowledge we now have regarding cancer control.

Other evidences of the Public Health Service concern in cancer control through the National Cancer Institute are familiar to most members of this conference. The tumor clinic at the Marine Hospital in Baltimore, the loan of radium to approved hospitals, the training of physicians in the diagnosis and treatment of cancer, the research fellowships, and the consultation service for States wishing to organize cancer-control programs are all phases of our current activity in this field. It was only in 1937 that the basic act was passed. Since then the Public Health Service has established the National Cancer Institute and on recommendation of the National Advisory Cancer Council has made grants-in-aid for cancer research. The annual budgets of the National Cancer Institute have varied from a high of $700,000 per year to about $500,000 during the last years of World War II, when we diverted to the war effort the major part of our scientific resources. For the present fiscal year, Congress increased the cancer budget to $1,772,000. At least one-half million dollars will be provided to aid cancer research in outside institutions during this fiscal year. Most of these grants are to research centers for the support of both fundamental and clinical research. Current projects in gastric cancer aided by Cancer Institute funds are as follows:

(1) Study under the direction of Dr. Leon Schiff, at the University of Cincinnati of (*a*) gastric excretion of radioiodide and its distribution in the body; (*b*) study of gastric carcinoma and chronic gastritis (current grant, $13,000).

(2) Study under the direction of Dr. Edward L. Howes, at Columbia University, of the relationship of undifferentiated epithelium and reticulin in the evolution of adenocarcinoma of the stomach produced by carcinogenic threads (current grant, $7,968).

(3) Study under the direction of Dr. Shields Warren, at Harvard University, of the pathologic aspects of gastric cancer and related lesions (current grant, $9,684).

(4) Study under the direction of Dr. C. P. Rhoads, Memorial Hospital for the Treatment of Cancer and Allied Diseases, of metabolism in patients with gastric cancer (current grant, $10,000).

(5) Studies under Dr. Owen H. Wangensteen, University of Minnesota, to identify "precursor groups," in which cancer of the stomach is developing (current grant, $8,900).

(6) Study under the direction of Dr. Robert Hebbel, University of Minnesota, of the relation of gastritis to carcinoma of the stomach (current grant, $2,100).

(7) Histochemical studies of the stomach in relation to cancer under the direction of Dr. David Glick, University of Minnesota (current grant, $3,950).

(8) A physiologic and cytologic investigation of the gastric-mucous barrier in relation to the gastric-cancer problem, and a study of the fasting gastric contents in patients as a basis for a possible diagnostic procedure, under the direction of Dr. Franklin Hollander, at Mount Sinai Hospital, New York City (current grant, $15,000).

(9) Study under the direction of Dr. John J. Morton, University of Rochester, of gastric secretions in patients with gastric cancer (current grant, $10,000).

Some of these projects have been supported by previous grants in addition to the current one. These grants represent a small, but sound beginning in a difficult sector of a baffling problem.

While the total Federal funds for cancer research up to now have been small, as compared with medical research grants to prosecute the war, the valid research proposals in cancer likewise have been few in number, of short duration, and not of large scope.

Yet there is a widespread and understandable public demand that this Nation, with its great technological competence, should turn its attention to the finding of the cause and cure of cancer, with the same vigor and ingenuity that were used to win the war. We may expect that this demand will increase; for with our aging population, more and more persons who once died from the diseases of childhood and early life will live into middle and old age to die of cancer. More and more families will see first hand the anguish of a loved one dying with cancer and will know the hopelessness of trying to save him. It will be impossible for them to understand why a Nation which has so perfected the art and science of destruction of life in war does not bend its full effort to improving its knowledge and applying

it widely and promptly to the saving of life from so dreadful a cause.

Why are not more great research centers prosecuting cancer research on a larger scale? Why do not more competent young scientists work on the cancer problem? These and like questions are posed to me constantly by interested citizens and legislators. The most frequent question is, How much money is needed to solve the cancer problem? Back of this last question there usually is the statement that we spent x billions of dollars to produce an atomic bomb, and the American people are willing to spend a comparable amount, or more if needed, to conquer cancer.

You scientists, who have struggled so long to secure funds with which to speed your pursuit of knowledge, and persons like myself, whose vicarious scientific satisfactions have come from putting a few more tools in the hands of eager investigators, are thrilled by this vista of bountiful aid. We are also sobered by the possibility that medical research as a whole may be discredited for years if vast sums of public moneys are accepted and spent with the implicit understanding that thereby the cause, cure, and prevention of cancer, or of any disease, is assured.

It is easy to understand the motivation, and all of us would concur in the objectives of those who assume that money alone will produce the desired result. Certainly we agree that without substantial funds the desired result is likely to be long delayed. A most praiseworthy purpose was responsible for the Pepper-Neely bill in the Seventy-ninth Congress, which authorized the impressive sum of $100,000,000 to bring together the world's cancer-research experts and, in the language of the bill, "coordinate and utilize their services in a supreme endeavor to discover means of curing and preventing cancer." Witnesses at hearings on this bill objected to the indefiniteness of administrative provisions and to its lack of relation to the existing program of the Government in cancer research and control. Although the bill did not pass, the hearings helped greatly to bring the problem of cancer before the public mind, to identify it as a national health problem, and to secure agreement that substantial amounts of Federal funds, with assured availability over a period of years, would be required to induce a sufficient number of scientific institutions and a sufficient number of competent young scientists to engage in the fundamental, long-time studies which most of us believe will be necessary before the scourge of cancer is ended.

You scientists, therefore, and others like you have the grave responsibility of forming a sound judgment and of giving competent advice to those who will be framing national legislative policy on this subject.

As a first fact in considering the background of cancer, I think we can agree that we cannot make a direct analogy between the manufacture of the atomic bomb and the discovery of a cancer cure. In 1940, the fundamental knowledge regarding atomic fission (and therefore, the probability that this knowledge could be applied to produce power or a deadly explosive) was much more complete than is our current knowledge of cancer prevention.

The cost of fabricating an atomic bomb was huge, yet the total cost of all the fundamental research by Einstein, by Rutherford, by Bohr, and by Fermi was very small, and it was not incurred with this specific object in view, quite the contrary. They were pursuing basic knowledge for its own sake.

Intensified studies, broadly based to find the cause and cure of cancer, probably will be most fruitful if directed towards the fundamental problems of cellular life, the interaction of groups of cells and of organ systems in this most complicated of all chemical and biologic structures, man himself.

With our limited total qualified scientific man power, with a great area of the unknown to be explored, with limited funds for all types of biologic research, and with many more objects of such research which have seemed to offer more promising (and more prompt) returns, relatively few research workers have engaged in cancer studies as such.

In the pursuit of the goal, it seems likely that we may not discover a route to the Indies, but, as accrued from the investment of Ferdinand and Isabella, there may be greater dividends in the discovery of an America on the way.

It is only the rare expedition of discovery, only the occasional research, that pays any dividends whatever. It has been said that only 2 percent of all industrial research is profitable at all, but the returns from that small fraction much more than balance the total cost.

I hope, also, that we shall not differ as to the principle that acquiring knowledge and applying it should be a part of the same process. Everyone agrees that we are applying only a fraction of our current knowledge about cancer to help those who die from it now. Ignorance on the part of the patient, lack of skilled doctors, lack of modern facilities staffed by competent experts, lack of money to pay for the best care, all result in needless cancer deaths.

Important though cancer may be as a public health problem, it is not separable from other major hazards with which our health agencies, Federal, State, and local, have been created to deal. The scientific tactics against tuberculosis, cancer, syphilis, infant mortality, mental illness,

or malaria will differ. Yet the over-all strategy is the same.

The basic philosophy which I am trying to expound is that the search for new knowledge concerning the cause, prevention, cure, and control of the major physical and mental diseases and impairments of man and the widespread application of such knowledge is of concern to our society as a whole. Therefore, it is an appropriate object of national action.

I urge you who are primarily concerned with gastric cancer to see your problems in this over-all setting of national health.

From what I have said you will realize that the Public Health Service has been searching for the elements of a sound policy in respect to cancer. After deliberation with our National Advisory Cancer Council, we jointly have adopted certain principles, which we shall put forward as a basis for discussion, and we hope as a basis for agreement in formulating a national course of action. The principles are as follows:

(1) The cancer problem is of such importance to the Nation's health that Federal action on a much larger scale than heretofore is greatly and urgently needed.

(2) Increased Federal support is needed not only for research into the cause and means of control of cancer but also for assisting States and local communities in applying more efficiently knowledge already acquired.

(3) The cancer problem is essentially a public health problem. While in its research phase, it must depend upon the widest variety of scientific disciplines, this, in itself, does not distinguish cancer from any other disease of man.

(4) Research is a basic tool and not an end of public health.

(5) A dissociation of fundamental research and practical application on any public health problem inevitably weakens the efforts of each.

(6) The United States Public Health Service has an extremely broad statutory basis for discharging appropriate responsibilities of the Federal Government in connection with the cancer problem. The Public Health Service has a background of experience and a nucleus of organization and physical facilities unparalleled anywhere in the world, as a resource to apply to the cancer problem in its broadest aspects.

(7) Experience has shown repeatedly that one of the great weaknesses of our national health effort is its dispersion, and the scattering of its programs and resources over a large number of different official agencies. All informed opinion is in agreement with the desirability, indeed necessity, of bringing the various elements of our national health program into a far more closely integrated framework of administration than now exists. This will become increasingly urgent as the health demands of the country come more nearly to exhausting its professional and scientific potentials.

(8) For these reasons, the policy of the Public Health Service is one of support to legislation which would provide for greater and more liberal assistance in dealing with both the research and control aspects of the cancer problem, but the Service could not lend support to Federal legislation designed to dissociate the several phases of the problem from each other by placing the research phase outside the administrative framework of the principal health agency of the Government.

In spite of the fact that much more could and should be done now, the outlook for cancer research and control in the United States is more encouraging today than it has been at any time in the past. With the return of peace to our country, our best scientific minds can once again follow constructive pursuits. Cancer constitutes a challenge to which both private and governmental agencies are today responding with new vigor. The efforts of each need to be combined. More tax money and more private money is being spent on cancer; more universities and hospitals are engaging in research; more State and local control programs are being established. But up to now all our sights have been set too low. The National Cancer Institute should have a modern cancer-research hospital and greatly expanded laboratory facilities to provide much needed space for enlarging studies already under way and initiating new ones, particularly those requiring a close correlation between the fundamental biologic sciences and clinical research. Much larger grants assured over a long period should be available to develop many other research centers and to support individual projects as well.

With greater interest being shown by private groups, additional sums of money are being made available for research. The American Cancer Society recently announced that between 3 and 4 million of the approximately 12 million dollars raised in its campaign this year will be devoted to research. The Alfred P. Sloan Foundation has given 4 million dollars to establish the Sloan-Kettering Institute for Cancer Research in New York City in connection with the Memorial Hospital for Treatment of Cancer and Allied Diseases. Another 4 million dollars was raised for that hospital through public subscription. These and many other efforts on a smaller scale are evidences that the attack on the cancer problem is being substantially broadened.

I have ventured to suggest to you a national cancer policy. Within the framework of this policy, we know that work on gastric cancer should have a prominent place. Early in its program, the National Advisory Cancer Council decided to exert special effort in gastric cancer because of its

high death rate and because of the lack of information on its causes, diagnosis, and treatment. Gastric cancer is one of the most complicated and important problems that face us today in the cancer field. Cancer is one of our most important health problems. Health is one of the most important national problems. To solve each requires the united effort of all. The Nation solicits your continued and increased help.

Chairman Brunschwig: Thank you, Dr. Parran. Before proceeding with the program, I should like to make a few announcements. (Announcement regarding luncheon.) We have foreign guests that we are happy to present to the conference:

Dr. V. V. Parin, Secretary General of the Academy of Medical Sciences of the U. S. S. R.

Dr. Michel Pobedinsky, of Moscow.

Dr. A. S. Serebrov, of the Institute of Oncology, Leningrad.

Dr. Rostislav Kavetski, of the Ukranian Academy of Sciences, Kiev.

Dr. P. R. Peacock, Director of cancer research at Glasgow Royal Cancer Hospital, Glasgow, Scotland.

Dr. Erik Laudboe-Christensen, Copenhagen, Denmark.

The following papers were then presented, as listed, without discussion:

Further Observations on the Genetic Nature of Gastric Cancer in Mice, by Dr. Leonell C. Strong, of Yale University.

The Pathology of Gastric Carcinoma in Mice, by Drs. Elsie McPeak and Shields Warren, New England Deaconess Hospital, Boston.

Experimental Hyperplastic Gastritis and Gastric Polyposis in Monkeys, by Dr. Clarence C. Lushbaugh, University of Chicago.

Observations on Gastric Atrophy after Liver Therapy, by Dr. Edward B. Benedict, Massachusetts General Hospital, Boston.

Pernicious Anemia and Tumors of the Stomach, by Dr. Leo G. Rigler, University of Minnesota, and Dr. Henry S. Kaplan, Yale University.

Studies of Patients with Gastric Cancer, by Dr. C. P. Rhoads, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City.

The Radical Surgical Treatment of Gastric Cancer, by Dr. George T. Pack, Gastric Service of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City.

An Attempt to Produce Malignant Transformation of Gastric Ulcers in Rabbits; a Preliminary Report, by Dr. A. C. Ivy and Almarose Cooke, Northwestern University and University of Illinois.

Gastric (and Salivary) Excretion of Radioiodine in Man (Preliminary Report), by Drs. Leon Schiff, C. D. Stevens, W. E. Molle, H. Steinberg, Carl W. Kumpe, and by P. Stewart, University of Cincinnati and Cincinnati General Hospital.

Concentration of Quinine in Gastrointestinal Cancers (Preliminary Report), by Drs. F. E. Kelsey and A. Brunschwig, University of Chicago.

The Cytology of the Gastric Fluid in the Diagnosis of Carcinoma of the Stomach, by Drs. George N. Papanicolaou and William A. Cooper, Cornell University and the New York Hospital.

FURTHER OBSERVATIONS ON THE GENETIC NATURE OF GASTRIC CANCER IN MICE [1]

By LEONELL C. STRONG, *associate professor, Department of Anatomy, Yale University School of Medicine*

INTRODUCTION

At the last meeting of the symposium on gastric carcinoma, data were presented which led to the following conclusions: (1) Gastric adenocarcinoma, as well as other types of neoplastic lesions and hyperplasias of the stomach, had been induced in mice following the subcutaneous injection of methylcholanthrene dissolved in sesame oil; (2) the untreated descendants of these mice continued to develop gastric carcinoma and other lesions spontaneously; (3) a genetic mutation had occurred on the "brown tagged" chromosome during the extent of the experiment of the injection of methylcholanthrene into both parents for many generations; and (4) this mutation was responsible, in part, for the development of gastric adenocarcinomas in the mice following the subcutaneous injection of methylcholanthrene.[2] These data, together with (1) the production of many physiologic disturbances, such as an increased growth rate, the attainment of giant adult body size, a precocious sexual maturity, and disturbances of fertility and fecundity, (2) many embryologic disturbances, such as situs inversus, dextrocardia, etc., (3) the induction of many somatic mosaics involving hair pigmentation (individuals which are somatic composites of two genotypes), (4) the establishment of an unstable physiologic state for the production of hair pigmentation, possibly due to an unstable genetic mechanism, and (5) the production of numerous germinal mutations, involving coat color, eye color, and distributional patterns of pigmentation, are convincing evidence that one of the effects of methylcholanthrene or one of its metabolites upon the organism is on the nuclear components and on the germ plasm bringing about germinal changes which are hereditarily established from their point of origin. Thus it is certain that a hereditary disease or a hereditary susceptibility to a disease, gastric cancer, and other biologically related lesions in the stomachs of mice, has been induced with chemical means. In this communication, it is our intention (1) to bring the experimental evidence bearing on gastric carcinoma in mice up to date and (2) to indicate the future development for a research program for the use of these mice. An extensive description of the various gastric lesions obtained, together with the investigation of the early histologic changes involved in the stomachs of mice that eventually give rise to a gastric lesion, will be discussed at some future time.

In order to orient attention on the particular gastric lesion being discussed, only two records are presented here. Female mouse G75 was born April 27, 1942. She died November 30, 1943, at 562 days of age. She had not received any experimental treatment since birth. She had, however, possibly been exposed to methylcholanthrene or one of its metabolites in utero, since her mother had been injected subcutaneously with 1 mg. of methylcholanthrene dissolved in sesame oil, on February 27, 1942. Autopsy of female G75 disclosed a solid tumor mass near the limiting ridge at the greater curvature of the stomach. This mass was 0.5 inch in diameter. One of the lymph nodes between the lesser curvature and the liver was approximately 0.25 inch in diameter. A second lymph node in the same region was also considerably enlarged. A description of this gastric lesion by Dr. Harry M. Zimmerman, together with his opinion of it, is as follows:

> Whereas the mucosa of the esophagus is intact, that of the cardia of the stomach is altered by carcinomatous change. The neoplasm is an anaplastic gastric carcinoma with ulceration, local invasiveness and distant metastasis. In part it is a definite adenocarcinoma, but there is some metaplasia with a slight tendency towards keratinization of the epithelium. Lymph vessels in the esophageal wall are invaded by the tumor. Many cells are in mitotic division. All coats of the stomach wall, including the serosa, are infiltrated by the neoplasm. A regional lymph node near the pancreas is partially destroyed by a metastatic mass of the gastric carcinoma.

Another record is from female mouse NHO 183224. She was born May 3, 1943, and on July 3, 1943, was injected subcutaneously in the right groin with 1 mg. of methylcholanthrene dissolved in 0.1 cc. of sesame oil. She died January 29, 1945. Autopsy disclosed discreet, solid, white nodules of tumors in the stomach, liver, diaphragm, peritoneum, ovary, and in the intestinal mesentery. The description of the lesion and an opinion of the tumor by Dr. Zimmerman are as follows:

> This again is an anaplastic adenocarcinoma which appears to have arisen from the cardia of the stomach. Although the esophageal wall is diffusely infiltrated by the neoplasm, the keratinized squamous epithelium which forms the mucosa of the esophagus is intact. There is considerable metaplasia in the tumor with a distinct tendency towards keratinization. Metastases are widespread to many different organs, but their microscopic appearance varies somewhat with the organ involved. Thus in the liver the tumor is predominantly adenocarcinomatous, whereas in the ovaries it is anaplastic and keratinizing. In the lymph nodes, on the other hand, these several microscopic pictures are all present.

The typical squamous carcinoma of the forestomach and the anaplastic carcinoma of the stomach, both of which tumors metastasize exten-

[1] This experiment was made possible by grants from The Anna Fuller Fund and The Jane Coffin Childs Memorial Fund for Medical Research.

[2] STRONG, L. C.: Genetic analysis of the induction of tumors by methylcholanthrene. IX. Induced and spontaneous adenocarcinomas of the stomach in mice. J. Nat. Cancer Inst. 5: 339–362 (1945).

sively throughout the abdomen, are not discussed here. Most of the lesions in the present series arise just anterior to the pylorus in the gastric mucosa. In only one case was the sphincter muscle of the pylorus itself involved in the lesion. The lesion grows in one of several ways, either as a polyp into the lumen, or as a spreading sheet just below the muscularis mucosa, or invasively into the muscular layers and beyond. The early tumors may be either cystic or solid. The terminal state apparently of the cystic condition was reached in male mouse 216733, which shows a double cyst coming from the gastric mucosa 1½ inches in diameter. On the surface of the cyst was a solid mass 0.75 of an inch long, the nature of which has not yet been determined. The relative frequency of these various types of lesions, all arising in the same anatomical relation to each other (indicated previously [3]), and the possible biologic relationship existing between them will be discussed at some future time.

MATERIALS AND METHODS

The origin of the mice used in the present work has been described, and the genetic relationship between the various sublines of the NH stock has also been discussed.[4] Similarly, the experimental procedures have been adequately discussed.[5]

RESULTS

To date, 540 mice have developed lesions in their gastric mucosae following the subcutaneous injection of methylcholanthrene. The lesions have occurred in mice from the F_5 to F_{18} generations inclusive. The data are given in table 1. Data on the average latent period between the subcutaneous injection of methylcholanthrene and the appearance of the gastric lesions are also presented graphically in figure 1. The figure shows that there has been a decline in the latent period from the F_3 generation onward. This decline, however, has not been uniform, as would be expected by genetic selection alone, but has occurred at two periods. The first decline, started in the F_3 generation, had reached equilibrium by the F_9 generation. Between the F_9 and F_{13} generations, there was a period of equilibrium in which the latent period for the development of gastric lesions did not change significantly. Again in the F_{14} generation a new decline for the latent period set in, and this has continued to the F_{18} generation. At the center of the period where equilibrium had been reached, showing a uniform response for the development of gastric carcinoma and its related gastric lesions, mice were outcrossed to mice of the untreated C57 inbred stock. These data provided material for the conclusion [6] that a mutation had

[2] [4] [5] See footnote 2.
[6] See footnote 2.

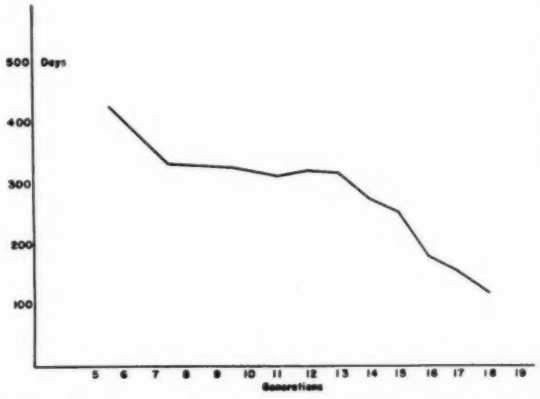

FIGURE 1.—Average latent period for the development of gastric adenocarcinoma following the subcutaneous injection of methylcholanthrene. The abscissa shows the generations of mice, the ordinate the average latent period in days.

occurred on the brown tagged chromosome, which caused these mice to give rise to gastric carcinoma following the subcutaneous injection of methylcholanthrene. The second precipitous drop in the latent period for the development of gastric lesions is therefore suggestive evidence that a new germinal mutation has occurred in a strain of mice whose ancestors for many generations have been injected with methylcholanthrene. This change could take place either at the old locus on the brown tagged chromosome or at some other locus. A considerable amount of work using the genetic technique of hybridization is indicated before a rational explanation of this new precipitous drop of the latent period is forthcoming. It is unwise to make a further outcross, however, before the latent period for the development of gastric carcinoma has again reached equilibrium.

TABLE 1.—*Appearance of gastric carcinomas and other lesions in mice following the subcutaneous injection of methylcholanthrene*

Generation	Number of mice	Average latent period	Generation	Number of mice	Average latent period
		Days			*Days*
5	1	471.0	13	88	321.9
6	4	463.0	14	74	283.6
7	7	283.3	15	62	256.6
8	6	399.3	16	63	190.1
9	8	255.7	17	25	158.7
10	10	388.1	18	2	129.0
11	60	312.8			
12	130	321.3	Total	540	

Figure 2 presents data on the incidence of spontaneous gastric carcinomas and biologically related lesions in the untreated descendants of mice whose ancestry has been injected with methylcholan-

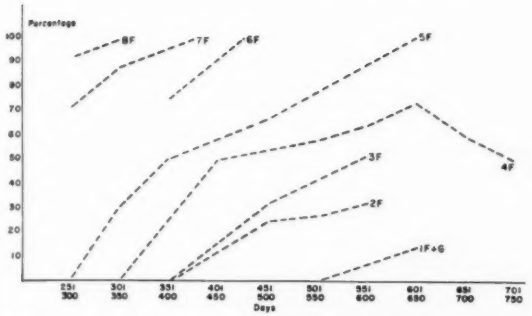

FIGURE 2.—Increased incidence of spontaneous adenocarcinomas of the stomach in nine successive groups of mice kept under controlled conditions but derived from mice that had previously developed adenocarcinomas of the stomach after being injected subcutaneously with methylcholanthrene. Abscissa, time in days; ordinate, percentages of mice showing spontaneous gastric adenocarcinomas.

threne for many generations. Five additional groups of one hundred twenty mice each have been added to the data bearing on this problem discussed at the former gastric cancer symposium.[7] The new data indicate that the incidence of spontaneous gastric mucosal lesions in the succeeding groups is coming earlier and earlier in life and in ever-increasing numbers. In the last group reported, 8F, all mice, both males and females, develop spontaneous gastric cancer, etc., by 325 days of age. The males, however, show a significantly higher incidence of stomach tumors than do litter-mate females. In this figure, data are presented for mice which may have been subjected to methylcholanthrene or one of its metabolites in utero.

In the 3FBr descent [8] the mice have been removed from a methylcholanthrene-injection history for more than 1 generation. Their ancestry, however, had been injected with methlycholanthrhene for 9 generations (from the F_4 to the F_{13}), At the present time, 12 generations of an untreated descent have been obtained (F_{14}—F_{25}), but mice only up to the F_8 generation have reached the expected gastric cancer age. In mice of the F_8 generation, the incidence of spontaneous gastric cancer is as high as it was in mice of the F_4 to the F_7 generation. It is thus becoming increasingly clear, although the necessary genetic outcross has not been made, that spontaneous gastric carcinoma in mice as well as susceptibility to the induction of gastric carcinoma by a subcutaneous injection of methylcholanthrene is also hereditarily determined. It would be of biologic interest to prove whether the 2 genetic mechanisms are the same or genetically independent of each other.

[7] See fig. 4, p. 348, of the paper by Strong, cited in footnote 2.
[8] Referred to previously on p. 353 of article by Strong, cited in footnote 2, although symbol was not used.

Another series of mice bearing upon the incidence of spontaneous gastric cancer has also been started. In this experiment, it was the intention to compare the incidence of these stomach tumors in mice where an overcrowding had been employed. In several series, six to seven mice (fig. 2) were kept in a single box, the boxes being of the same dimensions for all the series. The incidence of spontaneous gastric tumors was considerably reduced when the mice were overcrowded (10 to the box). This investigation, since it may throw some light on the problem of the origin and prevention of gastric carcinoma in mice, has been considerably expanded, and the results obtained will be discussed at some future time.

DISCUSSION

Until the biologic or pathologic nature of the series of stomach cancers and other related lesions in mice is more fully understood, it is perhaps futile to discuss them at length in terms of biology. As in other types of pathologic lesions, a considerable divergence of opinion concerning these lesions has already been expressed.

It seems reasonable to express the biologic opinion that these gastric lesions arising in the same anatomic position and relation to the gastric mucosa, even though they may show a multiplicity of end results, must be somehow or other organically related to each other. Some of these lesions are unquestionably neoplastic since they fulfill the criteria of malignancy of invasiveness and their ability to metastasize extensively; others are unquestionably adenomatous polyps, and still others are cysts. Genetically, these mice that give rise to variable gastric lesions are endowed with a considerable amount of biologic variability since they were produced through the process of hybridization. It is also clear that mutations are continually arising in the germ plasm of these mice and that this genetic process is also increasing biologic variability. Therefore it may be that the primary lesion is a single embryologic one, the nature of which has not yet been determined. Superimposed on this embryologic defect are the influences of biologic variability, and as a result of these biologic variants the end result in different mice is different.

In human gastric material, the pathologist must content himself almost exclusively with autopsy or terminal material. His opinions must be dependent upon the study of tissues obtained after or near the death of the individual. On the other hand in mice of the NHO descent (Brs subline), we have the opportunity of investigating not only the terminal stage of gastric adenocarcinoma showing invasiveness and widespread metastases but also by killing animals at all ages to investigate the earliest changes that lead inevitably not

only to gastric cancer but also to other gastric lesions which, although not suspected in human material, may be unquestionably biologically related to it.

CONCLUSIONS

New observations have strengthened a conclusion arrived at previously that a hereditary disease or a hereditary susceptibility to a disease, gastric cancer in mice, has been induced with chemical means.

A multiplicity of pathologic lesions arising just anterior to the pylorus of the stomach in mice are probably biologically related to each other, all being derived from the same or a similar embryologic defect.

This multiplicity of lesions all arising from the same or a similar biologic defect is probably the resultant of biologic variability of mice brought about by (1) the process of hybridization and (2) the induction of germinal mutations by methylcholanthrene or one of its metabolites.

THE PATHOLOGY OF GASTRIC CARCINOMA IN MICE

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In a study related to occurrence of gastric carcinoma in any animal, it is interesting to note that many reports (*1–9*) stress the rare occurrence of these lesions in the lower animals as contrasted with the high incidence of cancer of the stomach in the human being. Up to 1936 reports of gastric carcinoma in mice included 16 squamous-cell tumors (*5, 10–14*) and 3 adenocarcinomas (*5, 15*). In 1936 Bittner (*16*) recorded the finding of adenomatous tumors in 2 mice of strain I. In 1937 and 1938 Andervont and Stewart (*17, 18*) reported adenomatous lesions of the pyloric chamber of mice of strain I, stating that virtually all animals of both sexes had developed this lesion by the age of 8 months. They found similar but less extensive lesions in mice of 4 other strains.

In 1938 Wells, Slye, and Holmes (*6*) added 10 gastric tumors of epithelial origin, including 2 adenomas and 2 adenocarcinomas. Emphasis on the rarity of spontaneous epithelial tumors of the stomach of mice is brought out by the meager showing of a total of 14 cases in 142,000 necropsies on the Slye stock of mice.

In 1945 Strong (*19*) reported the increasing incidence of spontaneous adenomatous lesions of the pylorus in descendants of his selected NHO strain of mice. The original strains used in producing the NHO strain are all low-tumor. But one strain was reported as showing one mouse with an adenoma and four mice with adenomatous hyperplasia.

The two strains mentioned which are of interest now are strain I of Andervont and Stewart (*17, 18*) and the mice of Strong (*19*). From detailed studies on the strain I mice, Andervont and Stewart have concluded that the lesions in these mice are benign.

Recently we have had the opportunity to study histologically 93 of Dr. Strong's mice in which adenomatous gastric lesions occurred spontaneously and 149 of the selected NHO strain developing similar lesions following subcutaneous injection of 1 mg. of methylcholanthrene in 0.1 cc. sesame oil at the age of 60 days. Hereafter, the former group is referred to as the F series.

Both groups of mice show papillomas of the forestomach, 35 in the NHO strain and 17 in the F series. Six squamous-cell carcinomas of the forestomach are found in the NHO strain, an incidence of 4 percent. No squamous-cell carcinomas are present in the F series. There are two features in reference to these squamous-cell carcinomas that suggest that methylcholanthrene may have been the inciting agent: (1) The contrast between the presence of squamous-cell carcinomas in the NHO strain of mice, which received injections of methylcholanthrene, and the absence of these tumors in Strong's F series of mice, which were untreated; (2) the incidence of 4 percent in the NHO strain as compared with the recorded incidence of all tumors except lung tumors in this strain of less than 1 percent (lantern slides).

The gross appearance of the lesion in the glandular stomach of the mice of both the NHO strain and F series is presented on the basis of Dr. Strong's description, since our observations were confined to necropsies on 10 mice of the F series. These growths arose as polypoid masses near the pylorus, mostly on the greater curvature, but a few on the lesser curvature. Growth occurred outward into the lumen of the stomach or spreading in all directions along the mucosa. The spreading growth in many cases involved the entire pylorus, giving rise to complete encirclement of the pylorus with stenosis and sometimes almost complete obliteration of the lumen. In the microscopic section, the presence of the lesions on both sides of the stomach wall is probably due to this encirclement of the pylorus by the lesion. The cases which the senior author observed conformed to this group. A striking characteristic that was noted even before the stomach was opened, was the presence of cysts of varying size which appeared in the serosa of the stomach, chiefly along the greater curvature. These cysts in some instances bulged into the pancreas but always appeared to be limited by the serosal covering. It has been noted (*11*) that even malignant tumors form large projecting masses due to restraint for a long time, by such tissues as pleura, peritoneum, and blood-vessel wall.

The microscopic examination of the adenomatous lesions of both the NHO strain and F series of mice revealed glandular hyperplasia of the mucosa, usually confined to the pyloric portion of the stomach. But occasionally the hyperplasia extended almost to the junction of the glandular stomach with the forestomach. The form of the lesion is often polypoid arising rather abruptly, since adjacent mucosa appears normal. Other stomachs show less polypoid formation and more a thickening of the whole pyloric area of mucosa. The growths are composed of elongated, tortuous, and cystic glands. In some cases, these hyperplastic and distorted glands are confined to mucosa and submucosa, but in many instances they are found in the muscularis and serosa. The cystic glands bulge into the peritoneal cavity and pancreas. These cysts in some instances are partially filled with round, shadow forms which appear to be degenerating epithelial cells. Many cysts, even the deeply placed, when traced in serial section are found to communicate with the lumen of the stomach. The cells are mainly cu-

boidal and columnar, varying from medium height to very tall forms. In 35 NHO strain and 25 of the F series of mice there are present in the lesions masses of true squamous cells showing keratinization and intracellular bridges. The columnar and cuboidal cells usually occur in gland formation, with the retention of polarity and basement membrane. Very rarely a few cells appear to form solid nests. In most cases, the cells show reduplication in some of the glands, and polypoid projection of epithelium in the cystic glands is a common finding. The cytoplasm of the cells appears to contain a fairly large amount of mucus. The staining of the cytoplasm with eosin varies from intense acidophilic to light basophilic. The nuclei are hyperchromatic, large, round, or oval and are located in the middle or periphery of a cell rather than in the normal basal position. Mitotic counts made in the portion of the lesion near the lumen vary from two to eight per high-power field. The stroma varies in amount, apparently bearing some relation to the extent of inflammation. Simple erosion of tumors is frequent, but deep ulceration is not too common. Many cases of both the NHO strain and F series of mice show marked granulomatous inflammation.

Our findings would lead one to suspect that the inflammation is enhanced, at least, by embedded hair if not due to it. Reports (*20–22*) about the part played by hair in causation of ulceration of the rat's stomach are not in agreement. The inflammatory cells consist of polymorphonuclear leukocytes, lymphocytes, eosinophilic leukocytes, and large mononuclear cells. The cases with marked inflammation show some disruption of the stomach wall, but the purely hyperplastic lesion distorts the wall to a very small extent. In some cases, this proliferating connective tissue appears to carry the glands down into the muscularis and serosa. Associated with the inflammatory process in the stomach wall there is frequently an acute and chronic peritonitis of varying degree and in some instances acute or chronic pancreatitis. The pancreas, peritoneal lymph nodes, and liver in many cases show neither invasion nor metastases. But bulging of the cysts into the pancreas is very characteristic.

A few characteristics of these lesions can be demonstrated in lantern slides. We have also charted in tabular form some of the interesting facts determined from our study The first chart shows distribution of stomach lesions in each strain; the second shows the contrast in the age at which lesions were found in the two groups, NHO strain and F series; the third demonstrates a difference in occurrence of lesions in male and female mice; and the last table charts tumors of other tissues present in the animals with gastric lesions (lantern slides).

DISCUSSION

Our main purpose at this meeting is to present the problem involved in diagnosing the gastric lesions in mice which we have just presented. Two major questions arise from the histologic study of these lesions: (1) Are these lesions true tumors? (2) If tumors, are they benign or malignant?

Ewing's definition (*23*), "A tumor is an autonomous new growth of tissue," still expresses best the basic phenomena present in a tumor. Do our lesions fulfill this definition? We were led to consider the possibility of occurrence of an anomalous glandular formation. Our attention has been repeatedly drawn to the almost monotonous tendency of the cysts in these lesions to bulge into the pancreas. Too, in our review, sections on a few of the original strains were studied, and one, which had received no treatment, presented a lesion similar to lesions in the NHO strain and the F series of mice. Accessory pancreatic tissue is not at all uncommon in man (*24–28*) and may be composed mainly of ductules and glandlike tissue with little typical pancreatic tissue. The most common sites are the duodenum and stomach. Reports on such anomalous tissue in lower animals show a low incidence (*29–40*), and we found no reports of such tissue in mice. Since many cases in man are only incidental findings at necropsy, the known incidence in both humans and animals might be increased by careful search. Lantern slides on two human stomachs show appearance of anomalous ductlike and glandlike structures (lantern slides).

At this point, a definite decision as to classification of these lesions appears impossible. Further study of the F series at different age levels will help determine whether the lesions constitute an autonomous new growth of tissue or not.

If these lesions are tumors, what is the answer to the second question, whether lesions are benign or malignant? Ewing (*23*) states that infiltration of a tumor is the most important sign of malignant growth. In the lesions under consideration the question of infiltration can be answered only by determining whether or not the deeply placed glands in muscularis and serosa are evidence of invasion by an autonomous new growth. At present, such a decision must await further observations. Correlation of gross and microscopic findings with other studies on genetic factors, transplantation, and enzymatic activity of these lesions may eventually permit us to set up certain criteria that will enable us to diagnose these gastric lesions on a purely histologic basis.

SUMMARY

Comment is made on the rare occurrence of gastric carcinoma in lower animals as contrasted with the high incidence in humans. Special attention

is paid to reports on spontaneous occurrence of this lesion in mice. Both gross and microscopic characteristics of gastric lesions found in selected NHO mice injected subcutaneously with methylcholanthrene and similar lesions arising spontaneously in descendents of this strain are described in detail. The problem of diagnosis of these lesions is discussed.

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EXPERIMENTAL HYPERPLASTIC GASTRITIS AND GASTRIC POLYPOSIS IN MONKEYS

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INTRODUCTION

Often the byproducts of a research problem surpass in interest and implications the answer to the main question. Such was the case in the investigation we were asked by the National Defense Research Committee in 1942 to undertake. Our problem was to ascertain the extent to which the inhalation of oil fogs was a threat to the lungs of personnel screened from enemy observation by these clouds. Monkeys were chosen as the experimental animal because the anatomy and physiology of their respiratory tract most closely approximate those of man.

The effect of two oils was investigated. Because the armed forces at that time had not found the oil that met their requirements for use as a screening smoke, ordinary automobile oil (Pennoil S. A. E. No. 10) was used in the first experiment.[1] Shortly thereafter, this experiment was repeated using the oil chosen by the Chemical Warfare Service for screening purposes. This oil, designated as S. G. F. No. 1 oil, is a crudely refined shale oil of high viscosity and a specific gravity of 0.994. It was later found to be exceedingly rich in substances with the absorptive spectra of carcinogenic hydrocarbons. Four highly fluorescent fractions which showed strong absorption in the ultraviolet and near ultraviolet range were separated from it by chromatographic procedures. Detailed studies of the absorptive spectra of the fractions are planned in order to test the possibility that these represent carcinogenic hydrocarbons.

EXPERIMENTAL PROCEDURE

The monkeys used in these experiments were in a single shipment of 25 young adult *Macaca mulatta* (rhesus) monkeys.[2] Six were exposed to a fog of automobile lubricating oil, 7 to S. G. F. No. 1 oil; 7 were used in other experiments but furnished normal tissues for comparison in our experiments, and the remaining 5 served as normal control animals so that the effects of diet and environmental conditions on their life span in our laboratory could be observed. The last 5 animals are still alive and well today.

The fogs were generated by an atomizer[3] into a dynamic flow exposure chamber 7 feet high and 4 feet square, in which the monkeys lived throughout the course of the experiment. A centrifugal blower fan carried the oil into the chamber whence an exhaust fan removed it. The cloud was set up and maintained for half of each hour during the 24-hour day by means of an electrical timing device. The total exposure with each oil was 100 consecutive days in length. The monkeys, therefore, lived in the fog 12 hours of each day or a total of 50 whole days. The concentration of the automobile oil was approximately 132 micrograms of oil per liter of air, of S. G. F. No. 1 oil approximately 63 micrograms of oil per liter of air. The air flow through the chamber was about 2,400 l. per minute. These concentrations resulted in just visible mists.

The effects of the oil upon the lungs are being reported elsewhere. Remarkably little oil accumulated in the lungs. Oil composed 5–10 percent of the dry weight of the lungs after the hundred days of exposure. The reaction to it was slight and of no apparent serious consequence. The monkeys exposed to S. G. F. No. 1 oil, however, developed a fatal gastric lesion during the course of the exposure. Although this was an accidental discovery, the importance of which did not at first occur to us, the preceding exposure of monkeys to automobile oil and the subsequent observations on the other monkeys from the same shipment served as controls. No gastric lesions of any sort occurred in the six monkeys exposed to the automobile oil or in the seven monkeys treated and killed by various other toxic chemicals in our laboratory. The five unused monkeys gained weight and grew well on the various diets used and at no time showed signs of acute or chronic illness.

RESULTS

After the seven monkeys in question had been exposed to the shale oil for 4 weeks, they began to lose interest in their food, which at that time consisted of both white and whole wheat bread, various greens, apples, tomatoes, and occasionally peanuts and bananas. They began to lose weight slowly. Their fur became covered with oil, and much was shed. One monkey that lost weight more rapidly than the others apparently died of starvation after 44 days of exposure. Its stomach was of normal size, thin-walled, and microscopically normal. Sixty-seven days after exposure the second monkey died. No pathologic changes were found to account for the death or emaciation other than a small, shrunken stomach which because of severe post mortem changes was not examined histologically. The third and fourth monkeys died 4 and 10 days later. Again the only pathologic changes to account for the marked emaciation were in the stomachs. The walls of these stomachs were thicker than normal and

[1] The chemical determinations were made by Dr. C. E. Redemann, formerly chemist in the Toxicity Laboratory.
[2] Purchased from the Foundation for the Study of Infantile Paralysis.
[3] deVilbis atomizer, experimental model 360.

covered by thick mucus. The increase in size was apparently due to a moderate increase in both the mucosa and submucosa, although no histologic study was made of these stomachs because our attention and time were still devoted to the chemical analysis of the lungs.

The fifth monkey died after 97 days of exposure. This monkey was the most markedly emaciated, having lost at least half of its original weight. The fur was scanty and covered with oil. The stomach which was leather-bottle in appearance was filled with tenacious mucus. The gastric mucosa was thrown up in thick folds and had many low polypoid projections from it. Grossly visible cysts were present below the mucosa in dense, white, rubbery tissue that stiffened the gastric wall. Several areas along the lesser curvature were ulcerated. Microscopically, the changes consisted of an increase in the mucous cells, a complete absence of the parietal and chief cells, downgrowth of glandular epithelium through the muscularis mucosae, and the formation there of large epithelial-lined cysts. In many areas the epithelial cells were completely undifferentiated. The muscularis mucosae was thinned and heavily infiltrated by polymorphonuclear leukocytes. The submucosa was greatly thickened by edematous, young, fibrous, connective tissue. The ulcers extended to the muscularis mucosae. They were covered by a polymorphonuclear leukocyte exudate or were partially reepithelialized by a low cuboidal epithelium. These changes are illustrated in figures 2, 3, 4, and 5. Figure 1 is a photomicrograph of the stomach of a normal monkey for comparison. This monkey was starved for 4 days before it was killed in order that the size of the stomach would more closely approximate that of the stomachs of the other monkeys. The sixth monkey died 17 days after the cessation of the hundred-day-exposure period. Grossly and microscopically, the stomach of this monkey was identical with that of the preceding monkey.

These changes appeared to us very similar to those produced by Bonné and Sandground (*1*) in Javanese monkeys infested with a nematode, *Nochtia nochti*, and by Roffo (*2*) in rats fed various oils and fats. Since the former considered these lesions to be "gastric adenoma bordering on malignancy" and the latter "adenocarcinoma" on what appears to be inadequate morphologic grounds, every effort was made to keep our seventh monkey alive so that the ultimate fate of this lesion could be studied. This monkey when removed from the exposure chamber was emaciated and moribund but began to gain weight after 2 months on a diet consisting chiefly of milk, cabbage, dog chow, and nuts. After 6 months it appeared normal but was thinner than the remaining five unused monkeys. One year and a half

FIGURE 1.—Section of the stomach of a normal monkey starved for 4 days. Hematoxylin and eosin stain. ×

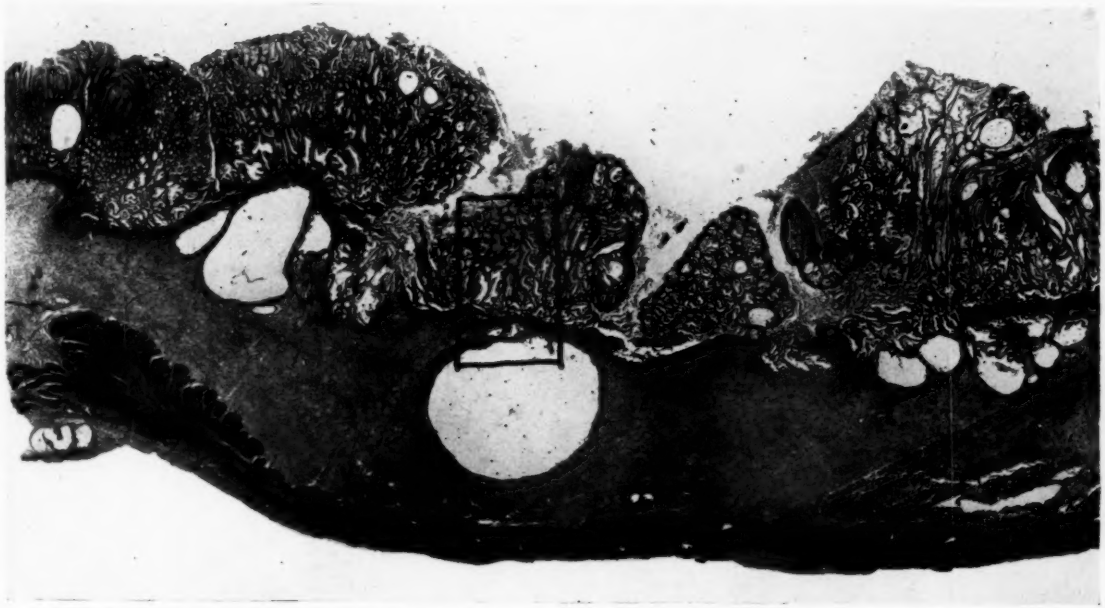

FIGURE 2.—Section of the stomach of a monkey that died after 97 days of exposure to S. G. F. No. 1 oil, showing the adenomatous appearance of the gastric mucosa, penetration of the muscularis mucosae by epithelial downgrowths, and the formation of large cysts in the hyperplastic submucosal connective tissue. Hematoxylin and eosin stain. × 8.

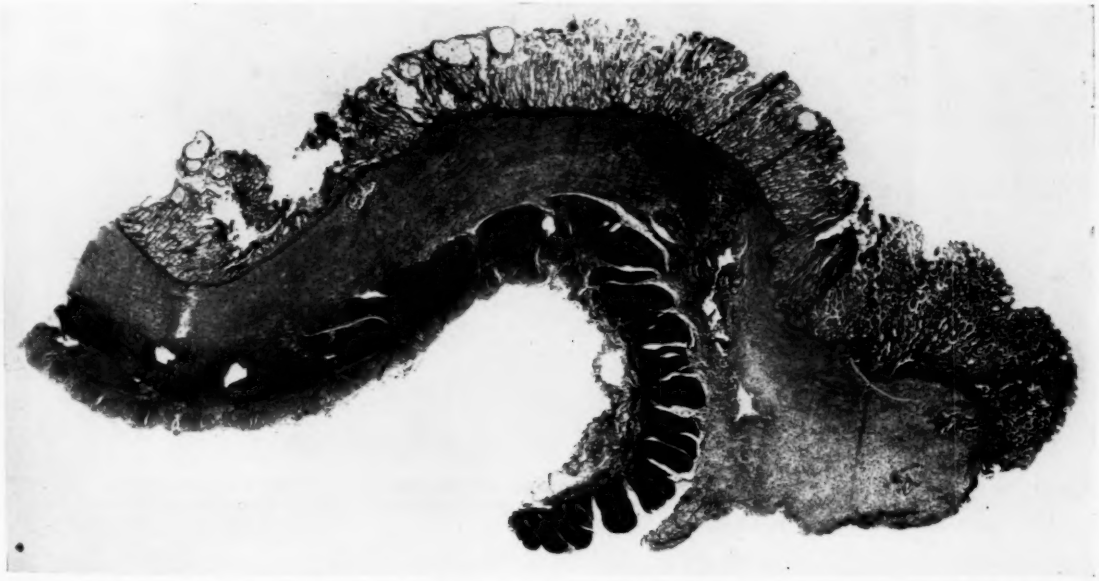

FIGURE 3.—Section of the stomach of a monkey that died 17 days after 100 days of exposure to the shale oil, showing an area of hyperplastic growth of mucous cells similar to figure 2 on the right, hyperplastic undifferentiated glands in the center, and an acute ulcer near the left hand side. Hematoxylin and eosin stain. × 8.

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FIGURE 4.—Area marked by the rectangle on figure 2, showing the hyperplastic features of the gastric mucosa, acute inflammation involving the muscularis mucosae, the penetration of the latter by glandular epithelium, and the low cuboidal character of the epithelium lining the large cyst. × 60.

FIGURE 5.—Section in figure 3, showing in greater detail an area of poor epithelial differentiation, and the destructive acute inflammation involving the muscularis mucosae. × 110.

after the exposure was completed, it was apparently in excellent health and was killed. No visceral abnormalities were found except for the stomach.

Grossly, this organ was more thick-walled than normal, but the mucosa appeared thinner than normal. No submucosal cysts were found. Microscopically, a typical severe atrophic gastritis was found. Large areas had a thin mucosa composed of sparse mucous glands (containing no parietal or chief cells) surrounded by an edematous lamina propria rich in lymphocytes and plasma cells (fig. 6, *A*). In other areas, scattered singly or in occasional islands, parietal cells were found (fig. 6, *B*). Throughout the mucosa and submucosa there was an enormous increase in number of lymphoid follicles (fig. 7). No evidence of neoplastic change was found.

DISCUSSION

Because of the accidental nature and the obvious inadequacy of these observations, few conclusions can be drawn. It appears, however, to be a fair assumption that, since 1 group of 7 monkeys chosen at random from a group of 25 developed severe gastric lesions which were fatal to 6, the treatment of this group with shale oil was responsible in some manner for the appearance of these lesions. This assumption is strengthened by the fact that none of the remaining 18 monkeys developed any gastric disease. Since the monkeys themselves, as well as the chamber in which they lived, became covered with the oil, much oil must have been repeatedly and continuously ingested or drained into the stomach from the upper respiratory tract. The appearance of a hyperplastic, adenomalike, gastric lesion in animals treated with an oil rich in substances with the physical chemical characteristics of carcinogenic hydrocarbons is of interest, especially since few gastric adenocarcinomas have been produced experimentally (Klein and Palmer (*3*), Stewart (*4*)).

The short induction period of less than 100 days for these lesions is especially interesting and may indicate that the gastric epithelium of monkeys is similar to that of man in its reactibility to irritants. These observations, along with those of Kennard (*5*) who found 15 instances of gastric

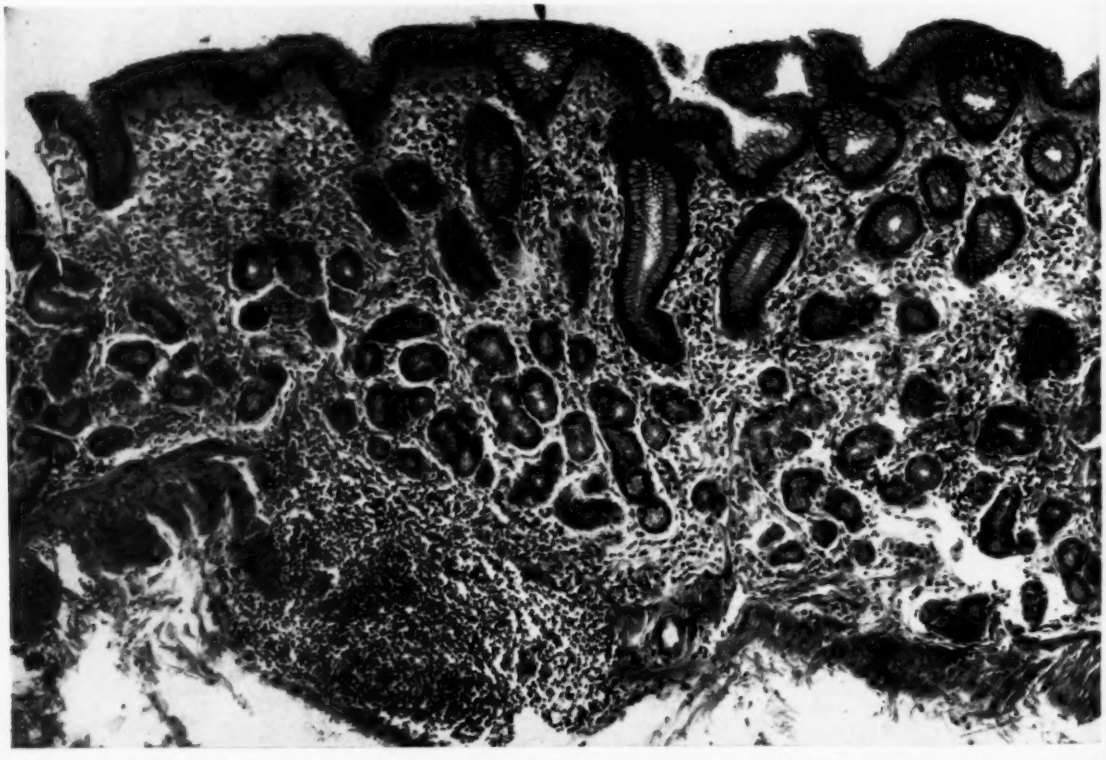

FIGURE 6.—*A*, Region of greatest atrophy in the stomach of the monkey killed 1½ years after exposure to shale oil. Hematoxylin and eosin stain. × 125.

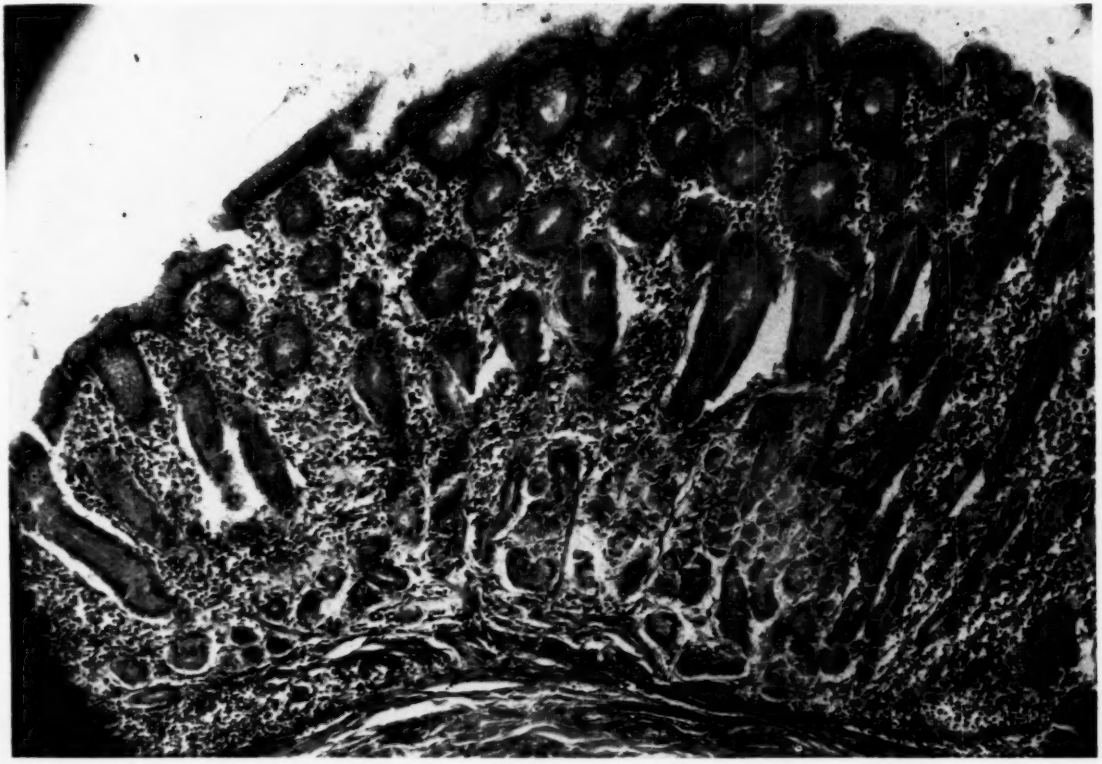

FIGURE 6.—*B*, Another area in this atrophic stomach showing a rare island of parietal cells (marked by arrow). × 100.

ulcer in 246 routine necropsies on monkeys and apes, raise the question whether the nonhuman primate might not be an excellent animal in which to study gastric disease. Certainly in the light of our observations an attempt to produce gastric cancer in monkeys appears warranted.

The presence of severe atrophic gastritis in the seventh monkey 548 days after it was removed in a moribund condition from contact with the oil, affords evidence that (1) the adenomalike gastric lesion of the similarly treated monkeys that died was not neoplastic but was a hyperplastic reaction of the gastric mucosa to prolonged irritation, and (2) after the removal of the stimulant, the hyperplastic changes were succeeded by those of atrophy. If these assumptions could be shown to be correct by repetition of this experiment, they would fortify the views of many (Ewing (*6*), Warren (*7*), and others) that hypertrophic or hyperplastic gastritis and atrophic gastritis are merely different stages in one general pathologic process. The relationship of these types of gastritis to neoplasia remains to be settled.

SUMMARY

Seven monkeys were exposed to a shale oil. Six died during or shortly after the 100-day exposure period. Hyperplastic gastritis, polyps, and penetration of the submucosa by epithelial growths were found in the two monkeys that survived the longest. The seventh monkey, alive 1½ years later, was killed and found to have severe atrophic gastritis. The possible significance of these findings is discussed.

FIGURE 7.—Fold of the atrophic stomach of the last monkey showing the large increase in number of lymphoid follicles. × 55.

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OBSERVATIONS ON GASTRIC ATROPHY AFTER LIVER THERAPY

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INTRODUCTION

Gastric atrophy has been recognized for many years. In 1935 Faber (*1*) stated that—

> in most cases of chronic atrophic gastritis there occurs a more or less extensive and very characteristic transformation of the surface epithelium into a goblet-cell epithelium, resembling that found in the intestinal canal.

In a study on the gastroscopic and pathologic findings in gastritis, Benedict and Mallory (*2, pp. 132–133*) noted:

> In the atrophic mucosa the significant feature is the progressive diminution of the epithelial elements, particularly at the bases of the glands. The glands become shorter; they lose their terminal convolutions; a gap appears between the base of the glands and the muscularis mucosae. Gradually they become more widely spread, and the intervening interstitial tissues show proportionate increase. Usually the muscularis mucosae [are] infiltrated with fibrous tissue and the layer of underlying loose areolar tissue often becomes narrowed and fibrous. This process may be accompanied by any grade of acute or chronic inflammatory infiltration. Metaplasia of the intestinal type appears in more and more numerous foci and eventually may entirely replace all proper gastric elements. * * * The gastroscopist and pathologist agree in defining atrophic gastritis as atrophy of large areas of the mucous membrane, seen gastroscopically as a pale, thin, mucosa with a network of easily visible blood vessels. Whether or not atrophic gastritis is the end-stage of an inflammatory process and therefore, a true gastritis, or the result of a vitamin or other deficiency and, therefore, better termed a gastric atrophy, is an unsettled problem. * * *. There is some evidence that both an inflammatory process and a deficiency factor may play a part.

In the series referred to, there was agreement between the gastroscopist and the pathologist in two-thirds of the cases of gastric atrophy. The discrepancy in the remaining one-third may be partly because in some cases the atrophy was confined to the antrum, which is not always well visualized by gastroscopy, and in other cases the atrophy may have been masked by a superimposed acute (superficial) gastritis.

For a long time gastric atrophy had been considered to be an end stage of chronic gastritis and an irreversible process. In 1935, however, Jones, Benedict, and Hampton (*3*) observed 5 cases of pernicious anemia in which, following specific therapy, evidences of atrophy and hypertrophy of the stomach both tended to disappear. In 1937 Chevallier and Moutier (*4*) observed that in atrophic gastritis under the influence of appropriate therapy, the anemia was cured, and the mucosa was improved in color. The mucosa increased in thickness, forming little protuberances and faint undulations, with the formation of folds. Blood vessels were no longer visible, the fragility of the mucosa diminished and then disappeared. In 1939 Schindler and Serby (*5*) studied 23 patients suffering from pernicious anemia, 9 of whom were seen before any treatment had been given, 14 were observed only after adequate treatment, and 3 were examined before and after treatment. According to their findings—

> all untreated patients presented superficial gastritis, superficial plus atrophic gastritis or patchy or diffuse atrophy. After treatment in 4 cases no marked improvement of the condition of the gastric mucosa was found, in 1 case there was definite progression of the atrophy, in 7 cases the mucosa of the antrum was found to be normal, in 1 case there was almost complete regeneration and in 4 cases all portions of the gastric mucosa became normal.

These authors concluded that in pernicious anemia two separate diseases of the stomach are present. Primarily, they postulated a dysfunction of the cells which produce the antianemic factor; secondarily, a degeneration of the surface epithelium with superimposed inflammation, which may or may not heal when the deficiency state is eliminated.

PATHOLOGIC DATA

Autopsy material on gastric atrophy is difficult to obtain for several reasons: (1) Patients with gastric atrophy seldom die in the hospital and come to autopsy. This is particularly true since the advent of liver therapy in pernicious anemia. (2) Patients with pernicious anemia who have come to autopsy in recent years have usually had liver therapy for an insufficient length of time to make possible the regeneration of their gastric mucosa. Since liver therapy was started in 1926, 8 patients suffering from pernicious anemia have come to autopsy at the Massachusetts General Hospital. Five of them had had no liver therapy or had had liver for only a few days before death. All showed gastric atrophy. The other 3 had had liver therapy for 6, 9½, and 14 months, respectively. All also showed gastric atrophy. The one who had had liver for the longest period, 14 months, also had a gastric polyp, and only a small amount of gastric mucosa close to the polyp was present for microscopic examination. The specimen was inadequate for complete study but did look atrophic. In 1934 Brown (*6*) studied the pathology of the gastrointestinal tract at autopsy in 151 cases of pernicious anemia and found chronic gastritis in all the 42 microscopic slides available. She used the term "chronic gastritis" to describe an interstitial infiltration of lymphocytes in the gastric mucosa, sometimes so marked that actual hypertrophy ensued. Intermingled with the lymphocytes were plasma cells and eosinophiles. Often many of the glandular tubules had disappeared, and fibrous tissue had replaced them. Some of the glands had dilated into mucous cysts containing many goblet cells. Twenty of the forty-two persons that had

chronic gastritis had had liver therapy (for unstated periods), but there was no noticeable change in the pathologic picture. Possibly none of them had had adequate treatment to make it possible for the gastric mucosa to regenerate.

Gastroscopic criteria for apparent improvement in the gastric mucosa are the disappearance of visible blood vessels, the return to a more normal color, and the reappearance of the gastric rugae. Such a return to a more nearly normal gastroscopic picture sometimes takes as long as 2 years. It is, therefore, not surprising that it has not been substantiated by autopsy material.

LOCALIZED GASTRIC ATROPHY

Gastric atrophy may occur as a localized or a diffuse process with or without pernicious anemia. Two thousand gastroscopies have been reviewed, beginning in 1933.

Localized Gastric Atrophy Without Other Pathology

Localized gastric atrophy has been seen in five persons without pernicious anemia or other disease. In two of these, however, there was a questionable gastric polyp. Follow-up gastroscopies in these persons have not been performed.

Localized Gastric Atrophy With Peptic Ulcer

In 18 cases, localized gastric atrophy has been found in association with peptic ulcer. The atrophy was almost always localized to the anterior wall, where blood vessels were readily visible, shining through the thin mucosa. In 1 of them, the gastric mucosa failed to show improvement 2 years after liver extract was given by mouth but did show improvement 2 years later after liver injections had been given intramuscularly at weekly or biweekly intervals. After adequate intramuscular liver therapy, the previously visible network of blood vessels was no longer seen. There were, however, increased reddening, edema, and adherent secretion throughout the body of the stomach, indicating a superficial gastritis. Some of this adherent secretion was by chance removed with the gastroscope as it was withdrawn. This was studied microscopically and confirmed the diagnosis of acute gastritis by the pathologic report of an inflammatory exudate. In another case of localized gastric atrophy associated with ulcer, the atrophy was seen in the proximal part of the hour-glass deformity. The distal part could not be visualized. In another case, the atrophy was in a gastric remnant following partial gastric resection for duodenal ulcer.

Localized Gastric Atrophy With Carcinoma

In carcinoma of the stomach, gastric atrophy occurs not infrequently. In only eight instances was it definitely mentioned. No doubt it was present many times but was not thought worthy of comment or was not noted because of the examiner's interest in the tumor. Moreover, the usual carcinoma of the stomach, which is obvious by X-ray, is not examined by gastroscopy.

Localized Gastric Atrophy With Superficial Gastritis

The occurrence of atrophy with superficial gastritis is fairly common but was specifically noted in the post-gastroscopic diagnosis in only nine instances. In four of these, it was definitely confined to the anterior wall; in one, it was patchy; in two, it was associated with gastric polyps; and in one, it followed 2 years after subtotal gastrectomy. In that case a posterior gastroenterostomy had been done previously, and severe superficial postoperative gastritis without atrophy had been observed by gastroscopy. These observations tend to confirm the findings of other gastroscopists of the association of polyps with gastric atrophy and of the possible occurrence of atrophy after superficial gastritis or after gastric resection.

DIFFUSE GASTRIC ATROPHY

Idiopathic Atrophy

Diffuse gastric atrophy has been observed in 20 cases. Although a number of these patients were examined more than once by gastroscopy, most of them had had either insufficient liver therapy, or there had been an insufficient lapse of time after the beginning of liver therapy to permit the drawing of any conclusions. There is some reason to believe that gastric atrophy may take several years to regenerate. Possibly some patients with atrophy have gone too long before the start of specific treatment to make regeneration possible. Four patients with idiopathic atrophy developed gastric polyps, one developed carcinoma of the esophagus, and another developed carcinoma of the cervix. Six tumors in twenty patients is an incidence of 30 percent. Could this high incidence of tumor in the stomach and elsewhere be related to gastric atrophy? In other words, is there even a remote possibility that a healthy gastric mucosa helps to protect other parts of the body as well as the stomach against tumor formation?

The following two patients with clinical and gastroscopic improvement are worth reporting in some detail:

Case 1. M. R., P. D. H. No. 14-471.—A 53-year-old housewife weighing only 108 pounds entered the hospital because of severe hematemesis 6 weeks previously. One transfusion had been given. The gastrointestinal series was negative. The blood examination was negative for pernicious anemia (hemoglobin, 81; red blood count, 4.13). Gastric analysis demonstrated 25 units of free hydrochloric acid one-half hour after histamine. Gastroscopy revealed a very ptotic and atonic stomach. There was no peristalsis. The pylorus was not visible. Very little of the antrum was visible. The mucosa throughout the

body of the stomach was slightly pale, smooth, and thin, with blood vessels visible on the anterior wall. In 1 area on the anterior wall, there was a somewhat mosaic appearance indicating some hypertrophic change. High up near the cardiac orifice on the lesser curvature, there were several areas of increased submucosal reddening indicating submucosal hemorrhage, and numerous pin-point erosions with active bleeding. Rugae were noticeably small or absent. Intramuscular liver therapy (10 to 15 units, 2 to 3 times a week) was begun, and gastroscopy was repeated 4 months later. The blood examination was again negative for pernicious anemia. The clinical improvement had been striking, but gastroscopy showed no change. The mucosa seemed very friable when touched with the tip of the gastroscope. The radiologist, however, reported thick folds and hyperactive peristalsis. Soon after this, a radical hysterectomy was performed for grade IV carcinoma of the cervix. Liver therapy was continued, and a third gastroscopy 5 months after the second demonstrated improvement, but the mucosa was still somewhat pale. Numerous rather small rugae were present. There was no sign of erosion, and no bleeding. The friable appearance was no longer noticeable. On the anterior wall, however, there was still a definite network of rather large veins. At this time, a gastrointestinal series showed very fine folds without evidence of ulcer or gastritis. Fourteen months later, after continued liver injections once a week, a fourth gastroscopy showed the mucosa to be a normal orange-red color, but with small rugae. No definite blood vessels were visible. Gastrointestinal series was negative. A gastric analysis revealed 26 units of free hydrochloric acid one-half hour after histamine. This was approximately the same reading as that obtained at the time of the first admission.

Comment.—This patient represents striking clinical and gastroscopic improvement after liver therapy. The improvement in the gastric mucosa was much slower than the clinical improvement and came only after 2 years of intramuscular liver therapy. X-ray examination was of interest because it did not agree with the gastroscopic findings; that is, the radiologist demonstrated thick folds at a time when the gastroscopist found gastric atrophy. This difference in findings is probably best explained by the fact that the radiologist studies the full thickness of the stomach wall without air inflation whereas the gastroscopist studies only the mucosa with air inflation. The carcinoma of the cervix apparently developed about the same time that the gastric atrophy was first observed.

Case 2. E. L. J., P. B. B. H. No. 61379.—A 65-year-old ex-prize fighter entered the hospital complaining of epigastric pain and pressure of 10 years' duration. The sensation of pressure came when the stomach was empty and was relieved by food or creamalin. A gastrointestinal X-ray was negative. Rugae were normal, and peristalsis was normal. Gastroscopy demonstrated, throughout the body of the stomach, a deep-red color with a blotchy, red, granular appearance. In the 7 o'clock position proximal to the angulus on the greater curvature, there was a marked verrucous appearance with active bleeding, friable mucosa, with erosions and adherent secretion. A diagnosis of superficial and hypertrophic gastritis with erosions and hemorrhage was made. A six-meal bland diet with liver and vitamin therapy was ordered, but liver was given only intermittently. Ten months later gastroscopy was repeated at which time peristalsis was sluggish, the mucosa on the anterior wall of the body of the stomach was pale and showed numerous blood vessels shining through. This appearance extended onto the lesser curvature and gave a blotchy appearance to a considerable part of the body of the stomach. A diagnosis of gastric atrophy was made with some residual superficial gastritis. It was felt that this represented a transition from superficial gastritis to gastric atrophy. Intensive intramuscular liver therapy was given twice a week, and at the end of 2 months the patient was very much better and stronger, with complete amelioration of symptoms. Another gastrointestinal X-ray was negative. Gastroscopy at this time demonstrated only a moderate superficial gastritis, with no evidence of atrophy. The patient continued liver therapy for a period of 2 or 3 months and then abandoned it. Seven months after the second gastroscopy, when he had been having no liver for at least 4 months, gastroscopy was again performed and revealed a pale anterior wall and lesser curvature, with numerous blood vessels visible. There was no evidence of any superficial or hypertrophic gastritis, but the gastric atrophy was more marked than ever. Blood examination at this time showed a hemoglobin of 14.5 gm.; red blood count, 4.1 million; smear, negative. The patient stated that he felt better when he was taking liver. Intensive intramuscular therapy was therefore resumed, and 8 months later gastroscopy was repeated. After a prolonged search, a few blood vessels were visible in one area on the anterior wall but were not very distinct. The mucosa was of a more nearly normal color, and the rugae were essentially normal. There was no erosion or ulceration and no evidence of superficial or hypertrophic gastritis. On the whole, except for one small questionable area of localized atrophy, there was a very marked improvement in the gastroscopic picture. Subjectively, the patient's strength was much better, and he had practically no digestive symptoms.

Comment.—This is a case of idiopathic gastric atrophy in which gastroscopy was performed five times. Transition from superficial gastritis to gastric atrophy was demonstrated during a period when the patient received very little if any liver therapy. Intensive liver therapy resulted in marked subjective and objective improvement. When liver treatment was allowed to lapse, the patient was subjectively worse, and the gastric atrophy became more marked. A resumption of intensive intramuscular liver injections again resulted in improvement both subjectively and objectively.

Gastric Atrophy Associated with Pernicious Anemia

Fifteen patients with pernicious anemia have been studied gastroscopically. One of these patients was examined only once by gastroscopy after 4 years of adequate liver therapy. Her stomach appeared entirely normal. Nine patients were not adequately examined before and after liver therapy to permit definite conclusions. One 57-year-old patient was studied before and 6 years after liver therapy and showed gastric atrophy both times. In spite of definite clinical improvement, there was no improvement in the appearance of the gastric mucosa. Six years should be an adequate period of liver treatment to result in regeneration of the gastric mucosa, if regeneration is ever going to take place. Apparently the gastric atrophy is irreversible in some cases. Three of the fifteen patients showed definite improvement following liver therapy, but the improvement was not continuous in all of them, there being some remissions and relapses.

Case 3. C. E. H., M. G. H. No. 14714.—A 46-year-old sign painter first entered the hospital in January 1935 because of weakness of 6 months' duration. He complained of anorexia and nausea, with numbness and tingling of his extremities. Gastric analysis showed no free hydrochloric acid. A blood smear was typical of pernicious anemia, with a red blood count of only 1.7

million. Gastrointestinal X-ray showed moderate prominence of the gastric rugae, but no other evidence of organic disease was noted. Gastroscopy revealed pallor of the mucosa, with a network of blood vessels easily visible, particularly in the fundus. In other areas, the mucosa was a fairly good red color giving a blotchy appearance. On the greater curvature near the antrum there was a nodular protuberance about 2 cm. long, 1 cm. wide, and raised above the mucosa about ½ cm. The gastroscopic diagnosis was gastric atrophy and pseudopolyposis. Two months later, after intensive liver therapy, there was marked clinical improvement and good appetite and strength. Gastroscopy revealed the mucosa to be practically normal, but with some granular appearance. On the greater curvature about 3 or 4 inches from the pylorus, there appeared to be a smooth protuberance, 1x1x2 cm., which did not disappear on air inflation and which was thought to be a true polyp or pseudopolypoid. No blood vessels were noted at this time, and it was felt that the mucosa was markedly improved, with no evidence of atrophy.

The patient was discharged home and followed in the out-patient department where he received adequate liver therapy. Nine months later, gastroscopy was repeated and demonstrated that the mucosa had regained its normal color throughout, and a questionable polyp in the antrum was again demonstrated. Liver therapy was continued, but no X-ray or gastroscopy was performed for 11 months, at which time a nodular, nonulcerating polypoid mass about 4 cm. in diameter was described and was felt to be probably a polypoid carcinoma. Although the mucosa was somewhat pale and the rugae were small, there was no definite evidence of atrophy. X-ray examination the next day confirmed the diagnosis of a probably malignant polypoid tumor in the midportion of the stomach. The patient was admitted to the hospital where a local excision of the tumor was performed, the pathologic report being adenocarcinoma, grade I. The pathologist made the following comment: "Over a distance of 3 centimeters, the normal mucosa is replaced by a layer of approximately twice the normal thickness. This consists of glands which maintain an approximation of the normal architecture though branching and secondary gland formation are marked. Throughout this region the cells are atypical in character showing no mucous formation, orientation of the nuclei and unusually numerous mitoses. At one point downward extension of the tumor through the muscularis mucosae is evident. An interesting feature is the extreme grade of 'acute gastritis' in the regions of the neoplastic involvement contrasted with moderate gastritic reaction in the normal mucosa. In the latter several islands of intestinal metaplasia are noted. The markedly polypoid character of the gross lesion proves to be due primarily to a marked edematous thickening of the submucosal connective tissue and only to a slight extent of epithelial overgrowth." A subsequent review of the microscopic sections showed definite atrophy about the base of the tumor with extreme metaplasia and marked infiltration and hemorrhage.

Liver therapy was continued and gastroscopy performed again 13 months after the operation. At this time, normal gastric rugae were present in most parts of the stomach, but in one area they appeared to end in a bulbous manner. On the greater curvature in the body of the stomach the folds presented a granular and slightly verrucous appearance. The findings were felt to be consistent with hypertrophic gastritis. The following day a gastro-intestional X-ray examination disclosed what was thought to be a broad-based polypoid lesion on the posterior wall of the stomach close to the cardia and probably malignant. Gastroscopic examination was again performed, and no recurrent tumor was demonstrable. In view of the X-ray findings, the gastroscopist felt that the patient should be operated upon again. The operation was not performed, however, as the radiologist was not certain, and the gastroscopist could not demonstrate the lesion. A year and a half later, the deformity became very marked by X-ray, and there was no doubt that the patient had an extension of the recurrent carcinoma. This was confirmed by exploratory laparotomy, which revealed an inoperable, recurrent carcinoma of the stomach, with metastases. Nine months later, the patient died at home. No autopsy was performed.

Comment.—In spite of intensive liver therapy for a period of 22 months, with subjective improvement in the gastroscopic appearance of the mucosa, this patient developed a grade I adenocarcinoma with the pathologic demonstration of definite atrophy around the tumor and marked intestinal metaplasia. This would seem to indicate (1) that in spite of adequate liver therapy and improvement by gastroscopy, the atrophy still persisted, and (2) that liver therapy was not adequate to protect against the development of gastric carcinoma. We cannot know, however, exactly when this low-grade carcinoma began to develop.

Case 4. E. D. S., M. G. H. No. 6073.—A 65-year-old street-railway operator entered the hospital in July 1934 complaining of dyspnea and weakness of 6 months' duration. There were numbness of his hands and toes and daily nausea and vomiting. The blood picture was that of pernicious anemia with hemoglobin of 45 percent and a red blood count of 1.38 million. A gastrointestional X-ray examination revealed an irregular filling defect showing evidence of craters involving the lower half of the stomach. The findings were those of carcinoma. Gastroscopy demonstrated a very pale mucosa throughout, with many blood vessels readily visible. Normal rugae were almost entirely absent. On the lesser curvature and posterior wall in the antrum of the stomach, there was a smooth, rounded, elevated lesion about 7 or 8 cm. in diameter, which was thought to be a large benign polyp with possibly malignant change. A diagnosis of gastric atrophy and gastric polyp with possible malignancy was made. After several transfusions, the patient was operated upon, and a gastric polyp was removed. The lesion was 15 cm. in length, and the pathologic diagnosis was gastric polyp with no evidence of malignancy. Intensive liver therapy was started, and 6 months later the gastroscopy was repeated, revealing improvement in the color of the mucosa, with, however, some areas of moderate pallor. Rugae were present and were nearly normal except for some irregularity and a pseudopolypoid arrangement in the antrum. X-ray examination at this time showed a small stomach with thickened rugae throughout. In the prepyloric area, there was no large lesion, but the distortion of the rugal pattern suggested small polypoid swellings. Another gastroscopy at about the same time demonstrated some increased reddening and two small erosions. There was no evidence of atrophy. A diagnosis of superficial gastritis was made.

The patient was then lost sight of for approximately 5 years, during which he had some liver by mouth and occasional injections. His previous symptoms recurred, and the typical blood picture of pernicious anemia with marked relapse was present. The gastrointestinal X-ray examination was repeated but showed no definite change since the last examination. The polypoid changes previously described were still present. Unfortunately, a gastroscopy was not done.

Comment.—This case demonstrated the marked gastric atrophy of pernicious anemia in which a very long, finger-like polyp had already developed before any treatment was begun. After excision of the polyp and adequate liver therapy, there was an apparent gastroscopic improvement in the mucosa.

Case 5. G. H. W., M. G. H. No. 158711.—A 43-year-old housewife entered the hospital October 19, 1938, because of epigastric pain, gas, nausea, and vomiting of approximately 18 months' duration. For about 10 years, there had

been weakness, dizziness, pallor, and heart pounding. A blood examination revealed the characteristic picture of pernicious anemia; an X-ray of the stomach demonstrated some thickening of the mucosa in the region of the cardia which had more the appearance of a thickened fold than of a polyp. Gastroscopy showed marked atrophy throughout, and many blood vessels were plainly visible; there was definite pallor and some areas of blotchy reddening. No polyps were demonstrable. After 6 weeks of intensive liver therapy, there was a moderate improvement in color, but the blood vessels were still visible. A third gastroscopy 3 weeks later showed continued improvement in color, but blood vessels were readily visible. Two months later, a fourth gastroscopy demonstrated continued improvement, but the blood vessels were less visible than formerly. Four months later, a fifth gastroscopy was performed, at which time the gastric mucosa was of normal color, and no blood vessels were demonstrable. Thus, it had taken 8 months of intensive liver therapy to bring about a return to normal by gastroscopy. The clinical improvement had been very noticeable after only 1 month of liver therapy. A sixth gastroscopy was performed 8 months later after she had been on inadequate liver therapy for a prolonged period. At this time, the mucosa was pale gray and smooth, rugae were absent, and many blood vessels were visible. For 2 years, she continued liver therapy, receiving 15 units intramuscularly every 15 days. For 3 years subsequently, however, she took no liver whatsoever and claimed she felt just as well without it. A seventh gastroscopy, 5½ years after the sixth examination and 3 years after she had no liver therapy, revealed a pale gastric mucosa, and numerous blood vessels visible on the anterior wall, lesser curvature, and posterior wall. The hemoglobin, however, was 13.1 gm., and the blood smear was essentially normal.

Comment.—This case demonstrates the gastroscopic improvement in the appearance of the mucosa during liver therapy, and the reappearance of atrophy after 3 years without treatment.

CONCLUSIONS

Gastric atrophy is a definite disease of the stomach. It may be in part the result of an inflammatory process or in part the result of a deficiency factor.

The diagnosis of gastric atrophy during life can be made only by gastroscopy.

Gastric atrophy may be localized or diffuse. As a localized process, it may occur with other diseases, such as ulcer or cancer, or mixed with other types of acute superficial or chronic hypertrophic gastritis.

As a diffuse process, it may be idiopathic or in association with deficiency diseases, notably pernicious anemia.

By gastroscopy there is evidence that in some cases the gastric mucosa improves after prolonged, intensive, liver therapy.

Pathologic proof of such improvement has so far been unobtainable.

The high incidence of stomach tumors in gastric atrophy is borne out in this series. The possibility is also mentioned that in gastric atrophy there is an unusually high incidence of tumor formation elsewhere in the body. Further statistical study would be necessary for confirmation.

It seems reasonable to postulate that the maintenance of a normal healthy gastric mucosa is of some help in the prevention of tumors of the stomach. The question is raised whether a healthy gastric mucosa could conceivably be of any protection against carcinoma elsewhere in the body.

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PERNICIOUS ANEMIA AND TUMORS OF THE STOMACH

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In the consideration of methods by which gastric tumors might be recognized at an early stage, roentgen examination with the barium meal is no doubt of first importance. To determine the utility of this procedure for diagnosis of very small tumors, it is necessary to examine symptomless individuals in whom neoplasms, if found, would be likely to be in an early stage. Because of the relative infrequency of gastric tumors in the general population, experience in diagnosis of small lesions would be gained very slowly and at great expense if some selection were not made. It seems desirable, therefore, to select a group of individuals who are more susceptible to neoplasms of the stomach than is the remainder of the population. For such a purpose, individuals with pernicious anemia serve admirably.

Within the past 15 years, increasing attention has been drawn to the coexistence of pernicious anemia and epithelial tumors of the stomach. That this association is more than accidental has been demonstrated by a number of large-scale statistical studies of both post mortem and living cases. Nevertheless, clinical recognition of this fact has been limited, and efforts at utilization of pernicious anemia as an indicator for the detection of gastric carcinoma in its early stages have been all too few. For this reason, it was thought worth while to review the evidence on this subject anew and to discuss its significance in gastric-cancer-detection programs.

STATISTICAL CONSIDERATIONS

The numerous individual case reports of coexisting Addison's anemia and gastric cancer have been collected by Cotti (*1*), Kaplan and Rigler (*2*), and others. These have little or no statistical value and are omitted from this discussion. Similarly, reports of multiple cases of this type have been published by Jenner (*3*), Strandell (*4*), Cotti, Murphy, and Howard (*5*), and others. In most of these cases, anemia had been present for years before the appearance of the gastric tumor, the longest interval being 17 years in the case cited by Miller (*6*). This observation was confirmed by Doehring and Eusterman (*7*), who found that the average duration of pernicious anemia prior to the onset of symptoms attributable to gastric cancer was 8.7 years in their series.

Comparison of the reports from the Mayo Clinic over a period of 25 years reveals a distinct increase in the incidence of gastric cancer in patients with pernicious anemia. Whereas in their first publication, by Giffin and Bowler (*8*), only 1 gastric carcinoma and 4 other malignant tumors were noted in a series of 628 cases, later studies (*9*, *10*) indicate a vastly different picture, the final series (*7*) revealing an incidence of 1.5 percent. The greatly increased life expectancy of individuals with Addison's anemia since the introduction of liver therapy is generally offered as an explanation for this apparent increase in gastric-cancer morbidity among them.

Not only cancer but also adenomatous polyps of the stomach have frequently been reported in association with pernicious anemia (*7*, *10*, *11*). Velde (*12*) found 6 such cases (14 percent) in a series of 42 pernicious-anemia patients, as contrasted with an incidence of 0.71 percent in a control series of 1,271 patients with other diseases. Such observations assume added significance when the apparently precancerous nature of gastric polyps is considered. In 1930 Miller, Eliason, and Wright (*13*) reported 8 personal cases and 24 others from the literature in which adenomatous gastric polyps had developed into carcinomas. Stewart (*14*) found carcinoma associated with 13 of 47 gastric polyps, and several other observations of similar character have since appeared (*15*, *16*, *17*). Accordingly, demonstration of a gastric polyp in association with pernicious anemia may be considered to approach in significance the demonstration of carcinoma per se.

These case reports, even in large series, are merely suggestive of a relationship between the two diseases. A statistical approach is essential to determine whether the frequency with which they are associated is greater than can reasonably be expected on the basis of chance alone. Several studies of this type have appeared, all of which have revealed a frequency of coexistence significantly greater than would have been predicted by probability.

Rambach (*18*) encountered 641 cases of gastric carcinoma and 50 cases of pernicious anemia in a series of 11,849 post mortem examinations. In 11 cases the 2 diseases were present together, an incidence roughly 5 times greater than that due merely to chance. Jenner (*3*) noted 5 gastric carcinomas, 4 benign gastric tumors, and only 1 extragastric malignant neoplasm in a series of 76 autopsied cases of pernicious anemia. Brown (*19*) found 12 gastric polyps (8 percent) among 151 cases of pernicious anemia in 18,200 autopsies.

In addition to the cases found at autopsy, some statistical studies on the morbidity of coexistent pernicious anemia and tumors of the stomach have appeared. Jenner (*3*) discovered 8 cases of gastric cancer in 181 patients with pernicious anemia. He computed the expected morbidity of gastric

cancer per decade among the living population of Amsterdam and found that the actual frequency in his pernicious anemia series was 12 times that in the "normal" population of comparable age. Van der Sande (*20*) similarly calculated morbidity statistics and likewise concluded that the 2 diseases were associated more often than chance alone would decree. Cotti (*1*) compiled all the published case reports in which pernicious anemia had been associated with a malignant tumor and found that the stomach was the primary site in 93 of 107 cases, or 86 percent of the entire series. Since cancer of the stomach represents only about 20 to 40 percent of all cancers in the general living population, the marked predilection for this organ in patients with pernicious anemia is another link in the chain of corroboratory evidence.

In an attempt to eliminate certain possible sources of error in previous publications on the subject, Kaplan and Rigler (*2*) studied all cases of pernicious anemia, carcinoma of the stomach, and carcinoma of the colon, cecum, and rectum recorded in a series of 43,021 consecutive autopsies performed by the Department of Pathology of the University of Minnesota. When corrections were applied for errors in the recorded diagnosis of pernicious anemia, an estimated total of 293 cases of this disease was available for study. Of these, 38 also had carcinoma of the stomach, 7 had gastric polyps, and 4 had carcinoma of the colon, rectum, or cecum. Statistical analysis revealed that only 12 cases of carcinoma of the stomach would have been expected. The probability that the observed number was due to chance alone was less than 1 in 1 billion. It is apparent, therefore, from all the foregoing evidence that some etiologic relationship must exist between pernicious anemia and gastric epithelial tumors.

THEORETICAL CONSIDERATIONS

The precise nature of this relationship, however, is still far from clear. On a purely hypothetical basis at least three possibilities can be enumerated: (1) Pernicious anemia directly produces a precancerous state in the stomach; (2) gastric cancer causes pernicious anemia; and (3) the two diseases are linked through a precursor or manifestation common to both.

It seems unlikely that pernicious anemia is a direct cause of gastric tumors, although conclusive proof to this effect is lacking. That the disease is often in remission at the time the cancer appears is a common observation, and Dyke and Harvey (*21*) observed several patients in whom adequate antipernicious anemia therapy for a number of years did not prevent the development of gastric carcinoma.

Likewise, the possibility that gastric cancer causes pernicious anemia can be quickly disposed of by recalling that in many instances where the two have been associated, the latter disease was present for a number of years prior to the appearance of the neoplasm. Because of the frequent occurrence, in patients with gastric cancer, of macrocytic anemias superficially resembling pernicious anemia, some confusion on this point appears to have existed in former years.

In a recent hematologic survey of 127 patients with gastric cancer, Oppenheim and his coworkers (*22*) found a state of anemia in 78, or 64 percent. The anemia was macrocytic in 25 cases, normocytic in 35, and microcytic in 18. In contrast with true pernicious anemia, most of the macrocytic group exhibited normochromia rather than hyperchromia. Moreover, a leukopenia was absent in all but 1, sternal-marrow studies did not show failure of maturation and the other characteristic features of pernicious anemia, free hydrochloric acid was often present in the gastric secretions, and a typical reticulocyte response to intramuscular liver extract could not be elicited in some of these cases. Inasmuch as evidence of extensive hepatic insufficiency had previously been found in many patients with carcinoma of the stomach (*23*), these authors were inclined to attribute the macrocytic anemias observed in their series to hepatic damage. No instance of true pernicious anemia was encountered in this study, a fact which seems at variance with the evidence presented herein. However, the incidence of pernicious anemia in other large series of gastric cancers, though significantly elevated, has still been only a few percent. Moreover, in a number of personally observed cases, patients with treated pernicious anemia in remission developed microcytic anemias due to chronic hemorrhage following the appearance of their gastric cancers. In such cases, the existence of an underlying pernicious anemia would have been completely masked except for the previous history. It is obvious, therefore, that in the series reported by Oppenheim et al., the few cases of pernicious anemia that might ordinarily have been expected could well have been absent on a chance basis alone or obscured by the development of some complication such as chronic blood loss.

It is, of course, theoretically possible for a diffusely infiltrating cancer to destroy the entire gastric mucosa responsible for the formation of "intrinsic factor" and thus produce "secondary" pernicious anemia. However, in the vast majority of cases in which the two diseases are found to coexist, the lesion involves only a relatively small portion of the gastric mucosa.

It is apparent, therefore, that the majority of cases in which the two diseases coexist must be explained in some other way. A number of features common to both conditions immediately come to mind as possible links between them

These factors include achlorhydria and achylia, atrophic gastritis, and heredity. A hypothetical diagram representing the possible relationships has been published by the authors (*24*).

Haring (*11*) suggested that the functional deficiency of the gastric mucosa which results in achlorhydria and achylia also acts as a stimulus to proliferation and finally to neoplasia, in a manner analogous to the development of goiter and adenomas of the thyroid in iodine-deficiency states. However, the frequency of achlorhydria is far greater than that of gastric carcinoma, indicating that it is certainly not a dominant etiologic factor.

Bloomfield and Polland (*25*) closely followed a group of 43 apparently healthy individuals with persistent histamine-refractory anacidity for a number of years and observed neither gastric cancer nor pernicious anemia in any member of the group.

Gastritis has been considered an etiologic precursor of pernicious anemia (*6, 26, 27*). However, Magnus and Ungley (*28*) carefully studied the stomachs of patients with pernicious anemia and found no inflammatory changes. Simple atrophy of the mucosa in the gastric fundus and corpus was the only consistent abnormality. It has been reported that on serial gastroscopic examination, the atrophy and "gastritis" seen in patients with pernicious anemia in relapse often disappears after adequate liver therapy (*29*). It is not likely that an essential etiologic factor in a disease would disappear in this manner. Moreover, Moschcowitz (*30*) has pointed out that achlorhydria and achylia frequently exist for years in the absence of atrophic gastritis, the latter appearing only after the other manifestations of pernicious anemia become apparent. Thus, the weight of evidence would indicate that gastritis is not necessarily a causative factor in pernicious anemia.

The alternative possibility that gastritis is a precancerous lesion has been expounded for years by Konjetzny (*31*) and others. The frequent demonstration of gastritis in cancerous stomachs naturally suggests a causal relationship, and Warren and Meissner (*32*) have pointed out the histologic similarity between the severe epithelial changes in some cases of gastritis and the morphologic appearance of known precancerous lesions elsewhere. Torgerson (*33*) studied the distribution of gastric cancers in unselected cases and in patients with associated pernicious anemia and found that the proportion of tumors arising in the fundus was distinctly higher in the latter group. Because of the known tendency of mucosal atrophy in pernicious anemia to affect the fundus and corpus more than the pylorus, he felt that this distribution of tumors argued for the precancerous nature of atrophic gastritis. However, such evidence is only circumstantial; the careful studies of Hebbel (*34*) and Guiss and Stewart (*35*) have failed to demonstrate that gastritis is more common in stomachs of persons with cancer than in those of other individuals of comparable age. Thus, although we cannot refute the possibility that chronic gastritis leads to gastric cancer, present evidence lends little or no support to this view.

The observation of familial tendencies in both pernicious anemia and gastric cancer indicates that common constitutional or hereditary factors may link the etiologies of the two diseases. Conner (*36*) first demonstrated the high incidence of achlorhydria in relatives of patients with pernicious anemia. Schwartz (*37*) reported that 18 percent of a series of patients with pernicious anemia also had relatives with the disease. The evidence for a familial component in the etiology of pernicious anemia has been summarized and discussed at length by Meulengracht (*38*) and by Moschcowitz (*30*).

Pernicious anemia and gastric cancer have been reported separately or together in several members and in more than one generation of many families. The cases of Borovanska-Felklova, as cited by Kohn and Reimann (*39*) and Thiele (*40*), are particularly striking examples of this type. Zancan (*41*), in a genealogic study of 74 pernicious-anemia patients, found evidence of 9 carcinomas among their blood relatives, of which 6 arose in the stomach. He traced a parallel series of relatives of gastric-cancer patients and found that in them incidence of gastric cancer was actually lower than in the group related to patients with pernicious anemia. While such observations are not statistically conclusive, present evidence, though inadequate, favors the thesis that the two diseases are linked through common hereditary influences.

Ivy (*42*) recently suggested that a study of blood groups in patients with these coexisting diseases and in their blood relatives might yield further information along these lines. In his opinion the fact that the gastric mucosa is a known storage site for the blood group-specific agglutinins may even have a direct bearing on the incidence of gastric cancer.

One additional hypothesis remains to be discussed. The increasing number of case reports of coexisting pernicious anemia and gastric cancer since the advent of liver therapy was attributed by Saltzmann (*43*) to the longer survival period of pernicious-anemia patients, a view that has been generally accepted. However, Teufl (*44*) rejected this explanation and speculated that liver extract itself might contain a weak carcinogenic agent which on prolonged administration could lead to cancer in susceptible individuals. This rather startling suggestion finds some experimental support in the work of Kleinenberg et al. (*45*), Steiner (*46*), and several others, who have

shown that certain fractions of the livers of both cancerous and noncancerous individuals, when injected into mice or rats, elicit malignant neoplasms at the site of injection in a small percentage of animals. It has been demonstrated by Strong and his co-workers (*47*) that animals genetically selected for resistance to the local effects of a carcinogen may exhibit secondary susceptibility to the same agent at a remote site. In the light of such evidence, the possible carcinogenicity of therapeutic liver extracts may well deserve further study.

EARLY DETECTION OF GASTRIC CANCER

Recent advances in surgery have made possible the salvage of at least 25 percent of patients with early, operable cancer of the stomach. Refinements in gastroscopic and roentgenologic technique have greatly improved the accuracy of diagnosis of such lesions. Were it not for the fact that early gastric cancer is generally asymptomatic, a considerable proportion of patients now dying of this condition could be saved. Thus, the chief problem in gastric cancer is becoming, more and more, its detection on a practical scale in asymptomatic individuals.

The most obvious way to attack this problem is to examine routinely, by roentgenologic or gastroscopic methods or both, all patients in the gastric-cancer-bearing age. However, morbidity statistics compiled by Collins, Gover, and Dorn (*48*) indicate that at any one time only 3 individuals per 1,000 in the living population over 40 years of age would be likely to have a carcinoma of the stomach. On the basis of these figures, any mass survey in which no selection of patients was employed would entail an enormous expenditure of time, effort, and money, with a very small yield of tumors. This prediction has been confirmed by the work of St. John, Swenson, and Harvey (*49*). These investigators, using a rapid fluoroscopic technique, examined over 2,400 asymptomatic individuals past 50 years of age and discovered only 2 carcinomas and 1 lymphosarcoma of the stomach. More recently, Dailey and Miller (*50*) studied 500 apparently healthy men 45 years of age or over and encountered no malignant tumors of the stomach. Such results emphasize the necessity of selecting patients for routine periodic examinations of the stomach on the basis of some pre-existing disease, symptom, or other criterion with which the occurrence of gastric cancer can be shown to be associated more frequently than in the general population.

The best indicator of gastric cancer is pernicious anemia; the presence of achlorhydria probably is the next best criterion. Two years ago, Rigler, Kaplan, and Fink (*24*) presented the results of serial roentgenologic and gastroscopic examinations in a series of patients with this disease. At that time, 211 patients had been examined 1 or more times; of these, 17 (8.0 percent) were found to have carcinoma of the stomach, and 15 (7.1 percent) had "benign" polyps. Since then, 48 new cases of pernicious anemia have been examined at the University of Minnesota, yielding 1 additional gastric cancer and 2 individuals with benign polyps. The summarized data are given in table 1. Comparison of these results with the morbidity, cited, of gastric cancer in unselected cases of comparable age reveals clearly the striking concentration of carcinomas of the stomach in patients with pernicious anemia.

TABLE 1.—*Clinical results*

Total cases of pernicious anemia examined	Carcinoma of stomach found		Benign polyps of stomach found		Total tumors of stomach found	
	Number	Percent	Number	Percent	Number	Percent
259	18	6.9	17	6.6	35	13.5

In comparing these data with other studies of routine examination of the stomach, it should be noted that there was no selection of symptomless individuals in these pernicious-anemia cases. It is true that the vast majority had no gastric symptoms, but in a few cases clinical evidences suggestive of gastric carcinoma were present.

Roentgen examination of the stomach at semiannual intervals has been made a routine procedure at the University of Minnesota Hospital in all patients with pernicious anemia. Some difficulties have been encountered in effectuating this program largely because of the inertia of both patients and physicians when symptoms are absent. Nevertheless, the program has gone forward, and some patients have now been examined as many as 12 times. Most of the gastric tumors have been discovered on the first or second examinations, but in a few instances later examinations uncovered the neoplasm.

Although no large-scale program of gastric cancer detection has yet been established at New Haven Hospital, even a casual survey of pernicious-anemia patients followed for a reasonable period reveals that several have developed polyps and carcinomas are known to have appeared in at least two such patients, one of whom is alive and well almost 2 years after gastrectomy.

The roentgen study has been pursued by means of fluoroscopy, "spot" films made of the mucosal pattern or when suspicious shadows were encountered, and by routine roentgenograms of the filled stomach. It is our impression that we should have overlooked several small carcinomas were it not for the series of roentgenograms which were routinely made. On the other hand, in all prob-

ability many of the small lesions, especially the benign polypi, would not have been discovered if fluoroscopic study with spot films had not been utilized. This method is expensive, time-consuming, and probably impractical for large-scale utilization. Fluoroscopy alone is likewise expensive because of the time required of the radiologist and may well be too inaccurate. It is possible that some method of rapid radiography of the stomach using the photofluorographic principle under controlled conditions, such as advocated by De Castro and his associates (*51*) in São Paulo, may well be a solution to this problem. It should be given a trial in this country.

The procedure we have used has been highly successful as a means of detection of small tumors. This has been particularly true of the benign polypi, lesions as small as 3 mm. in diameter having been discovered. The carcinomas detected by this routine procedure have mostly been larger in size, although in one instance the lesion was only 3 mm. in diameter and in another 10 mm. when first seen. Certainly our experience indicates conclusively that the routine examination of symptomless individuals by means of the roentgen ray will result in the detection of gastric tumors in an early stage of development.

A substantial number of rather large malignant neoplasms has been found in symptomless patients. Needless to say, the small lesions have almost uniformly produced no symptoms. Even in this relatively small number of patients, some salvage has been achieved, surgical removal of the carcinoma resulting in an apparent cure. On the other hand, as might be expected, a number of tumors, which were entirely without any symptom or manifestation other than the roentgen findings, were found to be inoperable owing to metastasis. In three cases the development of an extensive lesion from a relatively small, innocent-looking tumor was observed to take place in less than 1 year.

Unfortunately, pernicious-anemia patients represent a very small fraction of those susceptible to gastric cancer. Other indicators must be determined by careful clinical studies on large groups of variously categorized patients. A large-scale investigation of this type is now in progress at the University of Minnesota, the preliminary results of which are being reported by State, Varco, and Wangensteen (*52*). It is to be hoped that the final data will permit the Nation-wide establishment of selective gastric-cancer-detection programs from which a high yield of early tumors may confidently be expected.

SUMMARY AND CONCLUSIONS

Statistical analyses reveal that pernicious anemia and carcinoma of the stomach develop in the same individuals more often than would be expected on the basis of chance alone and must, therefore, be etiologically related.

Evidence pertaining to the nature of this relationship is still inconclusive but suggests that the two diseases are probably linked indirectly through the medium of some common factor. Among the possible factors to be considered are hereditary or constitutional tendencies, achlorhydria, gastritis, and liver therapy.

In contrast with the paucity of gastric tumors discovered in nonselective mass surveys, serial gastric examination of individuals with pernicious anemia has yielded a very high incidence of benign and malignant epithelial tumors of the stomach.

It is suggested that a search for other conditions etiologically related to or associated with gastric cancer is a necessary prerequisite to the establishment of practical, selective, mass surveys for the early detection of neoplasms of the stomach.

It seems desirable to effectuate a simple, inexpensive, rapid method for the routine roentgen examination of the stomach in symptomless individuals. Fluoroscopy alone probably results in a number of errors. The combination of fluoroscopy, "spot" films, and a series of roentgenograms of the filled stomach is expensive and impractical on a very large scale. The possibility of utilizing some method of photofluorography or cineroentgenography such as advocated by De Castro should be seriously considered.

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STUDIES OF PATIENTS WITH GASTRIC CANCER

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INTRODUCTION

For 5 years there has been in progress at the Memorial Hospital and, more recently, at the Sloan-Kettering Institute an intensive biochemical study of patients with gastric cancer. The frequency of the disease, the low rates of cure by surgical means, and the major nature of the surgery involved provide adequate reason for an active investigative effort. Nevertheless, in spite of the ample evidence that precise clinical studies under controlled conditions are useful, little work of this type has been done on patients with neoplastic disease.

The point should be emphasized that clinico-biochemical studies require the highest and most unselfish type of cooperation. Furthermore, they are immensely wasteful procedures. Since the welfare and comfort of the patient must be preeminent at all times, weeks and months of the work of many individuals of different skills are frequently lost because therapeutic procedures cannot be withheld from the patient until the investigations are completed.

The Gastric Service of Memorial Hospital, under Dr. George T. Pack, has not only provided the clinical material for the work here reported but also has been a generous participant in the studies. The willingness of these surgeons to modify preoperative care, to alter operative procedures, and to contribute to the postoperative study has been noteworthy.

The organization of the study warrants comment. A metabolic ward has been created in which patients may be maintained without charge for long periods. This ward is air-conditioned and has its own specially trained medical and nursing staff. A diet kitchen with its own staff of dietitians responsible for no other duties is available. Supplies of standardized food are provided. The laboratory is in charge of a biochemist, Dr. Nelson Young. Special facilities for record keeping and for tabulation of data are at hand.

CHANGES IN CARBOHYDRATE METABOLISM

The almost uniform malnutrition found in patients with gastric cancer is striking and demands explanation. The malnutrition bears no clear relationship to dietary intake, nor can any disturbance of digestion or internal absorption of food explain the progressive weight loss. For these reasons, patients with gastric cancer were suspected of metabolizing the foodstuffs absorbed by abnormal and inefficient mechanisms. The mechanisms which thus far have received the greatest attention have been those involving carbohydrates.

Under the experimental conditions adopted, the average concentrations of glycogen in the livers of fasted control subjects and those with gastric cancer were the same. However, when both groups were given orally comparable amounts of glucose before operation, the average glycogen concentration increased 3 times in livers of the control subjects but only 1.4 times in patients with gastric cancer. Among the possible explanations for this relative inability of the latter group to convert glucose to liver glycogen when a gastric carcinoma existed, a deficient activity of (1) insulin, or (2) certain adrenal cortical hormones was considered.

The former did not appear to be the case, since the administration of glucose and insulin (30 to 60 units) to a second group of patients with gastric carcinoma did not repair their limited hepatic glycogenesis. On the other hand, when adrenal cortical extract (Upjohn, aqueous) was injected during the glucose feeding of a third group of patients bearing gastric cancer, their average liver-glycogen concentration was found to be normal.

No significant reflection of a disturbed hepatic glycogenesis in patients with gastric cancer could be found by other clinical studies. Although their intravenous-glucose tolerance curves demonstrated mildly elevated average fasting and peak blood-sugar levels, the rate of disappearance of the injected glucose was not abnormal. Likewise, no significant alteration of the respiratory quotients of these patients before or after glucose injection was found.

CHANGES IN PROTEIN METABOLISM IN PATIENTS WITH GASTRIC CANCER

Previous studies in this laboratory revealed that regardless of adequate food intake there is a high incidence of hypoproteinemia in patients with gastric cancer. The disturbance has been shown to be amenable to some extent to preoperative feeding of large amounts of protein. Because of the hazard presented by hypoproteinemia in patients who require surgical procedures, it is important to know the mechanism which results in the abnormality.

To ascertain whether patients with gastric cancer could form plasma proteins in the presence of a sufficient nitrogen intake, nine patients were placed on a high protein diet as soon as possible after operation. Their regeneration of plasma protein was measured by electrophoretic techniques and by chemical (Howe's) method. Plasma volumes were determined by the use of Evan's blue. In six cases complete nitrogen-

balance studies were made. One patient with gastric cancer was thus studied for 27 days, the others from 11 to 15 days. Three patients with gastric ulcers served as control subjects under similar conditions.

These studies showed that in patients with gastric resection for ulcer total circulating plasma albumin and plasma globulin increased under the conditions of the experiment; in patients with gastric cancer they remained unchanged or decreased. Most patients with gastric cancer lost further plasma protein even though they were in positive nitrogen balance. The average amounts of plasma protein lost or regenerated are given in table 1.

TABLE 1.—*Average change during experimental period*

Group of patients with—	Total protein	Globulin	Albumin
	Gm.	*Gm.*	*Gm.*
3 operable carcinomas	−18.3	−13.7	−5.0
4 inoperable carcinomas	−22.5	−22.6	−.25
3 ulcers	+29.3	+7.1	+22.0

The A/G ratios were reversed in all cases of gastric cancer and in the two instances where plasma protein regeneration occurred in patients with cancer, it was due to the formation of globulin only. No increase of albumin levels could be demonstrated.

Methodological Points

These findings suggest that patients with gastric cancer do not regenerate plasma proteins because of a defect in the mechanism of protein synthesis or because of abnormal distribution of protein. It is of interest to note that the changes of the A/G ratio described in the literature are probably even greater than has been supposed. This is due to the fact that under certain circumstances alpha globulins may be determined by Howe's method as albumin. This finding led to a study of the value of the current methods of protein determination. A comparison was made between the results obtained by Howe's method, the falling-drop method, the methanol fractionation method, a new immunologic method of fractionation of Dr. Bacon Chow, and the procedure of electrophoresis.

Falling-Drop and Kjeldahl Methods

Results of blood protein determination by the falling-drop method have been compared in 69 cases with results of Kjeldahl determinations done within 24 hours of each other. In general, the falling-drop results were higher than the Kjeldahl results. Only 21.7 percent were found to agree within ±0.1 gm. Of those failing to agree within ±0.1 gm., 68.5 percent were too high, and 31.5 percent were too low. The greatest variations observed were not more than 1.4 gm.

The relation of the magnitude of this discrepancy with the blood protein level is shown in figure 1.

Electrophoretic Studies on Plasma of Patients with Gastric Cancer, of Patients with Ulcers, and of Patients with Leukemia

When electrophoresis of plasma is performed at pH 8.6, both gastric cancer and ulcer patients have low plasma albumin concentrations. Patients with gastric cancer have in addition some increase of plasma alpha globulins and fibrinogen. There also frequently are found small amounts of material more highly charged than albumin.

Plasma "albumin," as measured by Howe's method, corresponds roughly to the sum of the electrophoretic albumin and alpha globulins. In the plasma of patients free of gastric cancer, this relationship is well maintained. In patients with gastric cancer receiving hydrolyzate and high protein diets, however, the Howe "albumin" values often change markedly, quite independent of the electrophoretic albumin.

A series of analyses has also been made of plasma of patients with lymphatic and myelogenous leukemia, lymphosarcoma, and Hodgkin's disease. Their plasma albumin levels are low. There is also occasionally a large increase in gamma globulin. In four patients no change in plasma proteins was found after nitrogen-mustard therapy. A small amount of material moving faster than albumin was found in the plasma of few of the untreated patients. Some of these studies are being repeated when the material for analysis is brought to pH 4.0.

At pH 4.0, a definite component of mobility $= -2.70 \times 10^{-5}$ cm.^{2}/second/volt separates sharply from the plasma proteins. The plasma of patients with gastric cancer contains from 130 to 210 mg. percent of this material (average 170); normal individuals have from 60 to 120 mg. percent (average 80). Two patients whose tumors had been removed had plasma concentrations of 100 and 110 mg. percent. Patients suffering from malnutrition with ulcers and other noncancerous disorders, as well as patients with other types of cancer, are now being studied.

Alterations of Electrolyte Exchanges

The data previously presented on faulty hepatic glycogen formation in patients bearing gastric cancer and the repair of this defect by the administration of an adrenal extract have led us to investigate whether or not the disease is associated with some adrenal hormone imbalance. The demonstration of such a relationship would be of importance both in indicating new approaches to the

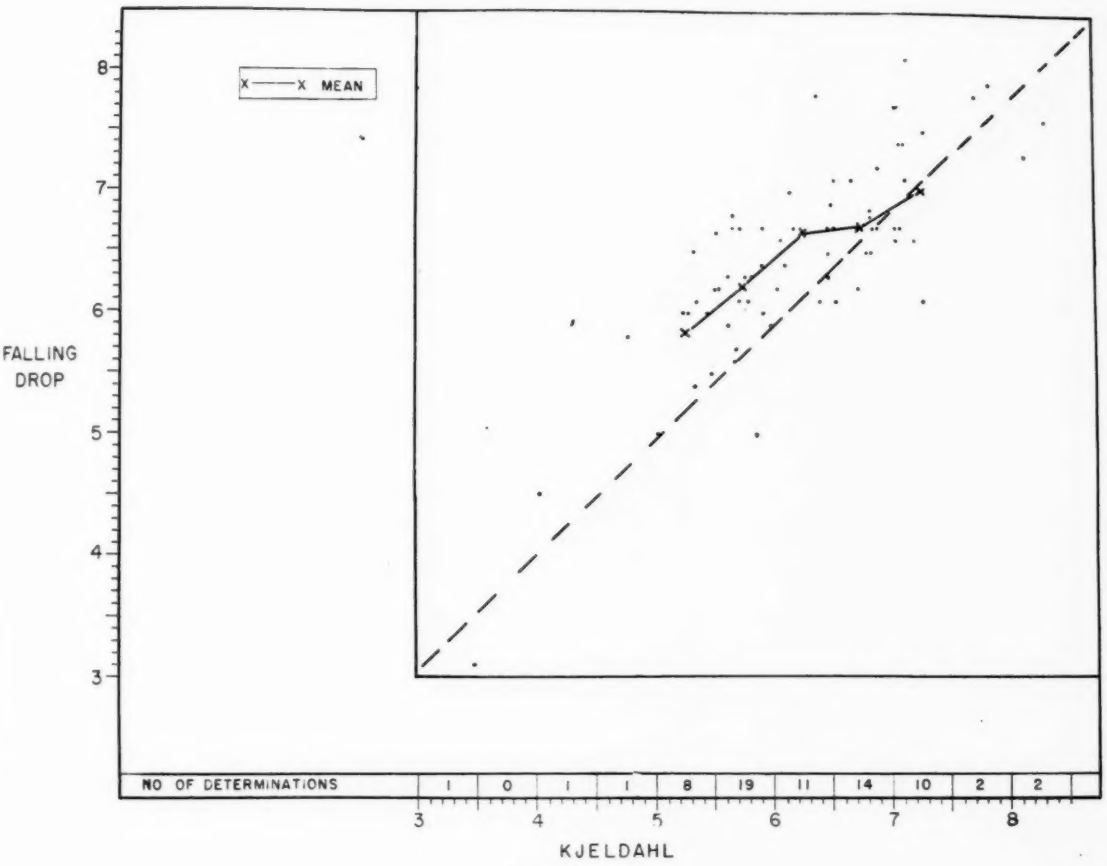

FIGURE 1.

basic problem of gastric cancer and in improving the medical management of these patients.

Disturbances in the distribution and balance of electrolyte and water are known to be associated with certain adrenal disorders. Isolated adrenal steroids have been shown to affect salt and water excretion and to correct the electrolyte changes which accompany adrenal insufficiency in animals and in man.

Several diagnostic procedures based on these changes have been found useful in cases of suspected adrenal disorder. These tests were supplied to patients with gastric cancer in order to investigate the connection, if any, between the existence of the neoplasma and an adrenal hormonal imbalance.

Kepler and associates have developed a test which is useful in the diagnosis of Addison's disease. Briefly stated, the test consists of giving fluid and sodium chloride equivalent to 2 percent saline for a period of 2 days. A large amount of water is given at the end of this period, and the excretion of sodium chloride and water is measured over a period of 4 hours. Thus far, the results of this test in patients with gastric cancer resemble more nearly those seen in Addison's disease than those present in any other disorder of known etiology; nevertheless, age, state of nutrition, and other factors known to be directly related to adrenal function also influence the results.

A normal diuretic response to water given without salt has been demonstrated in two patients with gastric cancer in whom it has been tested. This observation, made at the suggestion of Dr. H. W. Smith, is important since it makes improbable the involvement of the antidiuretic factor of the pituitary.

Cutler, Power, and Wilder have applied a salt-depletion test to demonstrate the impaired ability of patients with Addison's disease to conserve sodium when necessary. Two patients with gastric cancer have been subjected to this procedure, and

both gave similar responses to those given by patients with Addison's disease.

Soffer and co-workers have shown that in Cushing's syndrome, desoxycorticosterone acetate increases the excretion of injected sodium chloride under certain conditions in contrast with the decrease observed in normal subjects. A normal response to this test was observed in one patient with gastric cancer who had shown a reaction similar to that of patients with Addison's disease to the Kepler and Wilder procedures. This patient was in good nutritional condition and is the same individual who failed to regenerate plasma protein on a high-calorie, high-protein diet as previously shown.

Immediate postoperative salt intolerance is a well-established fact. Amounts of salt easily excreted by a normal individual lead to salt retention and edema if administered immediately after major surgery. It has been the experience here that patients with gastric cancer in the postoperative phase are particularly susceptible to salt "poisoning." Measurements of extracellular fluid by the thiocyanate method before and after operation combined with sodium-balance studies and measurement of plasma-sodium concentration provide no explanation of the fate of the sodium retained. It may be postulated that sodium has passed into the cells in significant amounts. The conclusive demonstration of such a shift would be of interest.

SUMMARY

This paper represents a condensation of the work of this group on patients with gastric cancer. This study, undertaken because of the high incidence and poor cure rate of gastric cancer, has yielded results which have helped to decrease postoperative mortality and morbidity and have increased the scope of resectability. Besides this practical gain, the studies have provided new knowledge of the systemic disease occurring in patients with gastric cancer. Whether this disturbance is of etiologic importance remains to be determined. Detailed knowledge of the condition is in any case most necessary for the proper management of these patients.

THE RADICAL SURGICAL TREATMENT OF GASTRIC CANCER[1]

By GEORGE T. PACK, M. D., *Gastric Service of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City*

The greatest margin for error in reporting end results for the treatment of gastric cancer may be found in the classification by the reporter of any given cancer of the stomach as operable or inoperable. The difficulty in correcting this fault is apparent when one realizes that three variable factors interplay in the pronouncement by any given surgeon that any cancer of the stomach is inoperable, viz: (1) The condition of the patient as regards his age, the coexistence of degenerative diseases, and the complications attendant on the presence of the cancer; (2) the extent of the disease, i. e., the degree of involvement of the stomach, the extension to and incorporation of neighboring viscera by the cancer, and metastases to regional and distal sites; and (3) the surgical philosophy, moral point of view, courage, and experience of the surgeon. In the large group of patients found to have generalized metastases or diffuse involvement of the liver and peritoneal lining, the recognition and acceptance of inoperability is obvious to any physician, but there are too numerous other instances in which the definition of inoperability may be subjected to careful evaluation, criticism, and even condemnation.

POINT OF VIEW OF THE SURGEON

It is not our purpose to formulate a set of rules governing the behavior of any surgeon in any given circumstance, but rather to present just arguments for extending the scope of operability for gastric cancer. The very nature of this disease, the infirm and often aged patients in whom it so frequently develops, and the radical character of the operations designed to combat it all conspire to make the surgical treatment of gastric cancer a hazardous venture for the patient and often an ordeal for the surgeon. With a knowledge of the inevitability of death from cancer of the stomach that is not treated, it seems unnecessary to state that no surgeon would refuse a patient the slightest chance for cure or even relief because of a fear of criticism for failure or an unnatural pride in low figures for operative mortality. Nor should any surgeon attempt to play God and decide arbitrarily that a certain patient with gastric cancer has lived a sufficiently long life or that he has so few remaining years of even normal life expectancy that operation at best would hardly be worth while. We must take care in our weighty decisions concerning the denial or offering of a chance for life to a patient that in our desire not to be the executioner we achieve the same end result by acting as an immoral judge.

[1] Read at the Gastric Cancer Conference, Chicago, December 5, 1946.

About a decade ago, Livingston and I (*1*) brought together for analysis and review the great body of published data on the treatment of carcinoma of the stomach recorded in the half century that had elapsed since the first successful resection by Billroth. For this purpose, more than 1,000 publications dealing with the subject were submitted to critical study. These represented, as nearly as could be readily ascertained, a virtually complete list of the recorded gastric resections from the world literature. Proper deductions, as drawn from this material, therefore, offered the most reliable conclusions obtainable up to that date.

At that time answers were sought to a number of specific queries which naturally arose: What was the life expectancy for patients with untreated gastric cancer? What proportion of those having the disease were given an extension of life, by medical, radiological, or surgical care? What is the nature of a definitive cure? Was there evidence concerning the nature and tempo of progress during that time? Upon what factors was this progress dependent? What accounted for failure to bring the benefits of excisional surgery to larger numbers? And to these might be added the further question: Was there reasonable hope, from facts and methods known, of obtaining in the immediate future, any materially larger number of definitive cures?

Any study of end results in the treatment of gastric cancer in terms of attained long-term definite cures resolves itself into an analysis of surgical methods and their value. For such a study it was essential to determine three points: (1) The applicability of excisional surgery or the percentage of the total number afflicted with the disease, for whom extirpation is feasible; (2) the risks involved in efforts to remove the carcinoma; and (3) the effectiveness of gastrectomy when this can be successfully performed. These points correspond to three questions for which the patient with the disease urgently seeks an answer: (1) Can the tumor be removed? (2) How much danger is involved in an attempt at its removal? (3) How certain will be the cure if I assume these risks and undergo the operation? Decision as to advisability of attempting a gastrectomy in a specific case must hinge in large measure upon these points, and the interpretation of the complete significance of the reported end results is dependent upon them.

The conclusions drawn from this study may be summarized here as representative of the conditions surrounding the diagnosis and treatment of gastric cancer in the United States a decade ago. These data (fig. 1) are presented in order to draw

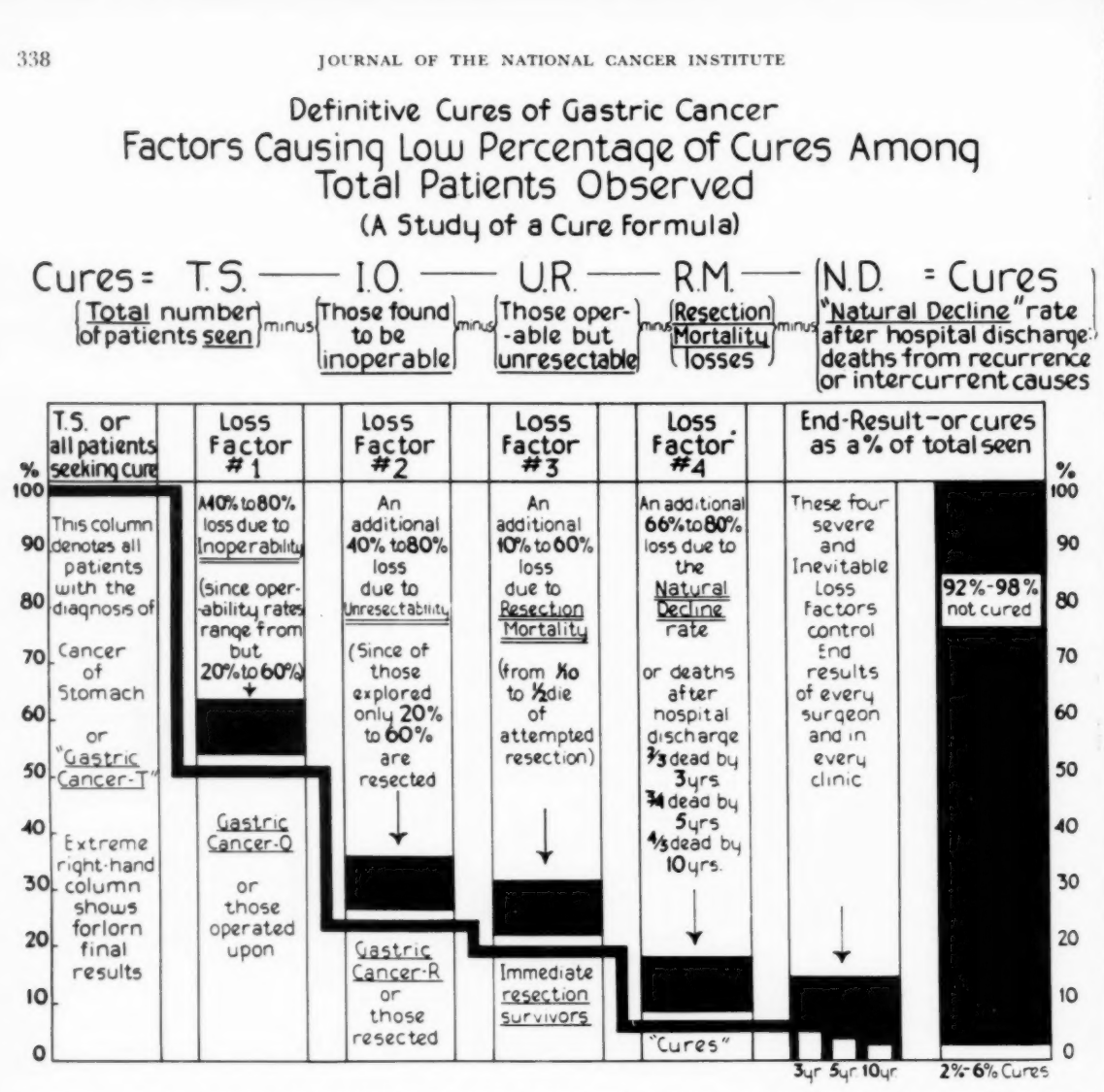
Definitive Cures of Gastric Cancer
Factors Causing Low Percentage of Cures Among Total Patients Observed
(A Study of a Cure Formula)
Cures = T.S. — I.O. — U.R. — R.M. — N.D. = Cures
Total number of patients seen minus
Those found to be inoperable minus
Those operable but unresectable minus
Resection Mortality losses minus
"Natural Decline" rate after hospital discharge: deaths from recurrence or intercurrent causes
T.S. or all patients seeking cure
Loss Factor #1
Loss Factor #2
Loss Factor #3
Loss Factor #4
End-Result-or cures as a % of total seen
%
100
90
80
70
60
50
40
30
20
10
0
This column denotes all patients with the diagnosis of Cancer of Stomach or "Gastric Cancer-T"
Extreme right-hand column shows forlorn final results
40% to 80% loss due to Inoperability
(since operability rates range from but 20% to 60%)
Gastric Cancer-O or those operated upon
An additional 40% to 80% loss due to Unresectability
(Since of those explored only 20% to 60% are resected
Gastric Cancer-R or those resected
An additional 10% to 60% loss due to Resection Mortality
(from 1/10 to 1/2 die of attempted resection)
Immediate resection survivors
An additional 66% to 80% loss due to the Natural Decline rate
or deaths after hospital discharge
2/3 dead by 3 yrs
3/4 dead by 5 yrs
4/5 dead by 10 yrs.
"Cures"
These four severe and Inevitable Loss Factors control End results of every surgeon and in every clinic
3yr 5yr 10yr
92%-98% not cured
2%-6% Cures

FIGURE 1.—Factors causing low percentage of gastric cancer cures in total patients observed. Average figures in the United States in 1937.

a proper comparison with the progress that has been made in the succeeding 10 years.

(1) The average patient with untreated gastric cancer was dead within 12 months after the onset of symptoms or was dead within 4 months after discharge from the hospital.

(2) Neither the size of the gastric neoplasm as revealed by clinical or radiographic study nor the lapse of time since the onset of symptoms offered a reliable guide for an estimation as to operability, for the reason that bulky adenocarcinomas, which fill a large portion of the gastric lumen, or slow-growing prepyloric tumors, which have caused symptoms over relatively long periods, alike may offer an excellent prospect for long-term cure.

(3) A satisfactory formula for the appreciation of attained cures of gastric cancer may be applied to any group of patients seen in any hospital or clinic as follows: Cures equal the total number of patients observed, minus the number of patients found to have inoperable gastric cancers, minus the number of patients operated on but found to have unresectable gastric cancers, minus the operative mortality or number of patients dying after resection of the cancer, and minus the number of patients dying in the 3-, 5-, and 10-year postopera-

tive periods, after which definitive cures become possible (fig. 1). The number and size of each of these loss factors precluded in 1936, and apparently for some time in the future, the attainment of large percentages of long-term cures among all patients seen.

(4) It was apparent from the relations of this cure formula that cancer of the stomach was not exclusively a surgical disease, for the role in deciding for or against operation was shared with the medical attendant, the radiologist, and others. The role of the medical attendant may exceed that of the surgeon in practical significance since the hospital service with high rates of operability will obtain more resultant cures with even inferior grades of surgery than will a hospital service with low rates of operability, no matter how excellent the surgical associates.

(5) Resectability or nonresectability is often ascertained with complete certainty only through surgical exploration. Laparotomy is here to be viewed as but a form of internal palpation; thus, resultant cure should not be measured solely against the total number of operations performed, for these include the management of a large number of surgically noncurable types of the disease.

(6) To perform a gastroenterostomy or other temporizing or palliative procedure for a resectable cancer is unwarranted because no author had reported (by 1936) an average extension of life from gastroenterostomy of more than 2 months, and the operative mortality for gastroenterostomy for cancer was as great as the operative mortality for attempted resection of a malignant tumor of the stomach. The life loss from immediate death following gastroenterostomy for cancer exceeded the total life extension gained among survivors, and any advantages of palliative gastroenterostomy were not to be measured in terms of life extension but in terms of symptomatic relief alone.

(7) The cure formula for resectable gastric cancer is: Cures equal resections performed minus operative mortality minus natural rate of postresection decline in survivors. It was noted that the patient with resectable gastric cancer had two hazards: (a) The resection risk; and (b) the postresection death rate from recurrence or natural death. The former was under surgical control while the latter rested largely in the hands of nature and could be but little influenced.

(8) Responsibility for establishing proper conditions for gastric-cancer surgery is largely an institutional problem; it is an ethical principle that institutions admitting patients with this disease in numbers should provide for their concentration in proper surgical hands, allow for the use of special surgical teams, and furnish the necessary special equipment.

(9) No surgeon, who is unqualified or who has not the full intent to resect a gastric carcinoma if a resectable tumor is encountered, has the moral right to operate on a patient with gastric carcinoma.

(10) Resectable gastric cancer is a numerically common condition, for necropsies have revealed that even at the time of death from gastric cancer approximately one-fourth of these tumors were still confined to the stomach or to the stomach and immediately adjacent lymph nodes.

(11) The operability rate may be referred to as the hospital or community index, while the resectability rate may be referred to as the surgical index. These two indexes either alone or in combination define the resultant cures attained, and a low index in either case identifies the cause of a low rate of resultant cures and reveals whether the medical or the surgical standard should be held accountable.

(12) In 1936 it was estimated that from two-thirds to three-fourths of gastric cancers were unresectable when first seen at the hospital or clinic. For approximately 60 to 75 percent of patients with this disease, surgery offered not the faintest hope for cure.

(13) With only 3 exceptions, no American clinic in the historical range of surgical therapy until 1936 had ever reported more than a total of 100 gastrectomies for cancer.

(14) Except where gastric resections were performed by specially trained surgeons or surgical teams working under ideal conditions, the operative mortality was excessive, and definitive cures proved numerically few. The resection mortality before 1936 in surgical centers performing large numbers of gastrectomies for cancer averaged 17 percent, while that for the casual surgeon or in clinics reporting small numbers of resections was found to average approximately 30 percent.

(15) Where malignant tumors were still confined to the stomach at the time of gastrectomy, 5-year cures reached as high as 50 percent of all patients upon whom resection was performed.

(16) At no time in surgical history up to 1936 and at no point in the world had the definitive cures of gastric cancer ever exceeded 5 percent of the total number of patients with the disease.

(17) Approximately one-third of the immediate survivors of gastric resection for cancer were alive at the end of 3 years; one-fourth were living at 5 years; and one-fifth were living beyond 10 years from the time of discharge from the hospital.

(18) The percentage of long-term cures for resectable cancer equaled or exceeded that obtained in the treatment of cancers of the tongue, cheek, tonsils, thyroid, brain, lung, esophagus, intestines, gall bladder, liver, prostate, ovary, and many other varieties of malignant neoplastic diseases.

In another statistical study published 10 years ago, Gallo and I (*2*) revealed that in a thousand patients with cancer the culpability for delay in es-

tablishing early diagnosis and instituting early and appropriate treatment was the fault of the patient in two-thirds of the instances but was the fault of the physician first consulted in the other third. It was mandatory at that time that the educational efforts should be directed not only towards the layman, who was entering the age at which gastric cancer might occur, but also towards the general practitioner, who usually encounters the patient at the time of the first complaint of indigestion.

In an effort to detect early gastric cancers even before symptoms become apparent, several studies were made in the form of elective radiographic examinations of stomachs of apparently well people in the cancer-bearing age. Dr. F. B. St. John and associates found 3 unsuspected gastric cancers in a consecutive series of 2,400 such X-ray examinations. As an effort to increase the salvage of patients with this disease, one might compare the possibilities offered by an increase in the radical nature of gastric surgery which has occurred largely through the same decade. For example, cancers of the gastric cardia, which were formerly considered inoperable because of their location in the stomach, may now be removed either by total gastrectomy via the abdominal route or by transthoracic, transdiaphragmatic cardiectomy with an intrathoracic esophagogastrostomy. If these operations were routinely done for patients with cancers in the gastric cardia, they would offer 150 of 2,400 patients with the disease an opportunity, at least, for cure.

The great improvement in end results in the treatment of gastric cancer which has been made during the past decade cannot be attributed to any studies dealing with the etiology of the disease. The betterment may be attributed to the following four factors:

(1) An improvement in the earlier diagnosis of gastric cancer due to increased alertness on the part of the public through education on cancer and through better medical facilities for recognition of the disease.

(2) A greatly increased number of surgeons in the United States are now qualified to perform the usual subtotal gastrectomy for cancer, in consequence of which the operation has much wider employment with the extension of the possibilities of cure to many more people.

(3) The patient has been made infinitely safer for surgical treatment of gastric cancer by improvements in preoperative and postoperative care. Metabolic deficiencies existent in the patient with gastric cancer, such as impairment of liver functions, disturbances in the fluid and electrolyte balance, and the almost constant hypoproteinemia with the many complications that follow this condition are now generally recognized, and the means of treating them are readily available and understood. Chemotherapeutic measures have been responsible for the lessening of complicating infections. Wound disruption is an extremely rare occurrence, and early ambulation of the patient lessens the mortality from such complications as pneumonia, thrombosis, embolism, and cardiovascular collapse.

(4) The extension of radical surgery in the treatment of gastric cancer has increased the scope or possibility of cure for many additional patients. The evolution of these surgical techniques has taken place largely in the past decade. Extension of radical surgical treatment of gastric cancer has progressed in three ways: (*a*) By the bold sacrifice of adjoining or contiguous viscera that may be involved by the gastric cancer. For example, in addition to the gastrectomy, segments of the left lobe of the liver, the pancreas, the spleen, and the transverse colon are frequently removed. These adjacent organs are sometimes so intimately adherent to the cancerous segment of the stomach as not to be separated from it by dissection; a removal with the diseased segment of the stomach increases the possibilities for cure. (*b*) By removal of the entire stomach, if the cancer involves the major part of the organ or has metastasized to lymph nodes extending along either the lesser or greater curvature of the stomach to such an extent that a wide margin of excision cannot be made safely with preservation of any portion of the organ. (*c*) For those cancers of the gastric cardia that involve the abdominal esophagus or extend into the thoracic esophagus, the surgeon may extend an abdominal incision intercostally into the thoracic cavity and by transecting the diaphragm convert the thorax and abdomen into a single

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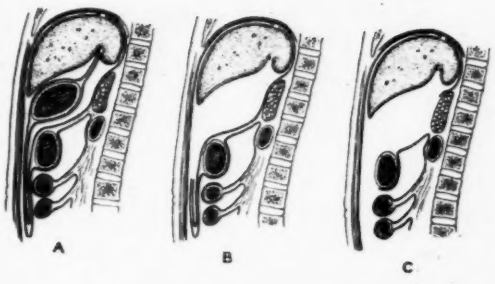
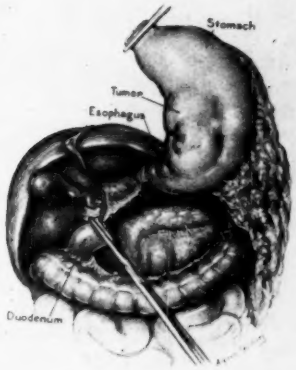
FIGURE 2.—*A*, Sagittal view of abdomen to show ligamentous attachments of stomach; *B*, Same after gastrectomy without removal of great omentum; *C*, Same after total gastrectomy with removal of great omentum and serosal lining of lesser bursa.

FIGURES 3–7.—Technique of total gastrectomy. Figure 3, The duodenum has been transected after ligating the right gastric, the gastroduodenal, and the right gastroepiploic vessels and after resecting the omentum along the reflection over the transverse colon. Figure 4, Exposure after cutting the left leaf of the triangular ligament of the liver and reflecting the left lobe of the liver forward. Interrupted mattress sutures between esophagus and jejunum have been placed with the viscera widely separated. Jejunum is being slid into position. Figure 5, Retrocolic type of anastomosis and the lines of incision into esophagus and jejunum are shown. Figure 6, A right-angle kidney clamp prevents reflux of gastric contents into esophagus. The third layer of posterior sutures is in place. Figure 7, The peritoneal flap is sutured below the line of the anastomosis, and the lateral jejunojejunostomy has been completed.


A
B
C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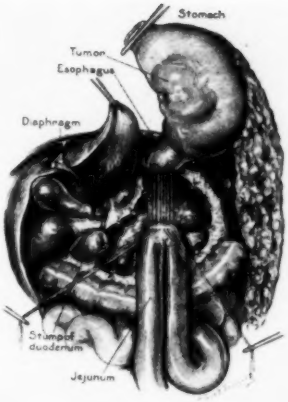
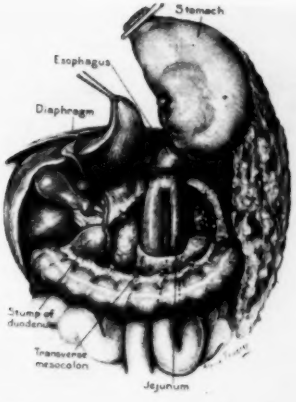
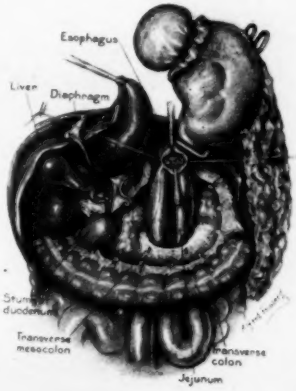
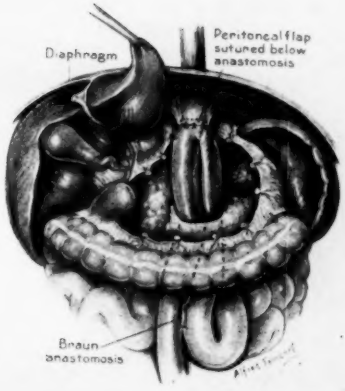
Tumor
Esophagus
Duodenum


Stomach
Tumor
Esophagus
Diaphragm
Stump of duodenum
Jejunum


Stomach
Esophagus
Diaphragm
Stump of duodenum
Transverse mesocolon
Jejunum


Esophagus
Liver
Diaphragm
Transverse mesocolon
Transverse colon
Jejunum


Diaphragm
Peritoneal flap sutured below anastomosis
Braun anastomosis

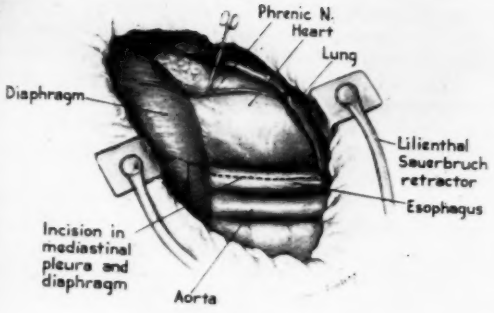
cavity in which resection of the esophagus and stomach may be performed with reconstruction of gastrointestinal continuity by an intrathoracic anastomosis.

In the Gastric Service at Memorial Hospital we have performed approximately 50 total gastrectomies for cancer. The operation (see figs. 2–7) includes a removal not only of the entire stomach but also of the adjacent lymph node-bearing regions as well, which include all the lymph nodes along the lesser and greater curvatures of the stomach, the greater omentum in its entirety, the parapyloric and retropyloric lymph nodes as well. In some instances, the peritoneum of the lesser omental bursa is stripped off with the specimen. The duodenal stump is closed, and the abdominal esophagus, after mobilization, is used for anastomosis to a loop of jejunum. The jejunal loop is brought up either in front of the colon or through the mesocolon to effect an end-to-side anastomosis with the esophageal stoma. The anastomosis is fortified by suturing a flap of diaphragmatic peritoneum anteriorly and posteriorly below the suture line in order to suspend the jejunum and to give additional strength to the anastomosis. A lateral anastomosis or enteroenterostomy is done in order to provide a short-circuiting of the bile and pancreatic juice between the proximal and distal jejunal limbs and in order to provide a suitable egress for any swallowed food which enters the proximal jejunal limb.

The operative mortality for total gastrectomy is 20 to 30 percent as compared with 8 to 12 percent for subtotal gastrectomy. The chief complications of the operation have been of pulmonary origin rather than infections in the peritoneal cavity. These patients have certain metabolic deficiencies during the postoperative state, but this has not been a great handicap to the individual patient. After proper time for adjustment, the jejunal loop serves most satisfactorily as a substitute stomach, and the patient usually can enjoy a full meal wihout appreciable discomfort. The organ is not essential for life, and such a complication as severe anemia is not encountered so frequently as one might anticipate in view of the important role this organ ordinarily plays in hematopoiesis.

The 8 to 10 percent of patients with cancer involving the gastric cardia are no longer classified as incurable, because the surgeon is now able to pursue an upward exposure of the cancer-bearing segment to include the cardiac end of the stomach and the abdominal and thoracic esophagus so as to carry the resection high, thereby insuring complete removal of the tumor and adjacent lymph nodes. (See figs. 8 to 13.) Dr. William Welch, in his chapter on cancer of the stomach in Pepper's Textbook of Medicine, published 3 years after Billroth performed the first successful gastrectomy in human beings in 1881, established certain criteria for the successful resection of gastric cancer, one of which was that the neoplasm should not extend beyond the stomach proper. A half century elapsed before this dictum was corrected, and surgeons elected to remove a liberal segment of the esophagus by the combined abdominal and thoracic approach. A small exploratory upper-left mid-rectus incision is made in order to ascertain the presence or absence of hepatic and peritoneal metastases, the extension of the cancer to regional lymph nodes, the mobility of the cancer, and the amount of distal uninvolved stomach available for subsequent anastomosis. If exploratory findings warrant continuance of the operation, the incision is then extended upward through the costochondral cartilages and laterally in the seventh intercostal space (fig. 8) to intercommunicate the thoracic and abdominal cavities. The diaphragm is split in a radial direction down to and including the crura (fig. 9). The stomach and terminal esophagus are mobilized in the usual surgical fashion (fig. 10), and the cancer-bearing segment is widely excised (fig. 11). If the distal half of the stomach is normal, it may be mobilized and drawn into the chest for anastomosis with the severed end of the esophagus. This union is accomplished by an end-to-end type of layer closure supplemented usually by a free omental graft to insure protection for the line of sutures. In 3 instances a total gastrectomy was done by this route, and the jejunum was then brought into the chest and anastomosed with the esophagus, once by an end-to-side anastomosis supplemented by an enteroenterostomy, and in 2 other instances by the Roux-en-Y technique whereby the distal end of the severed jejunum was anastomosed to the esophagus within the chest, and the proximal jejunal end was anastomosed by an end-to-side procedure with the distal jejunal limb at a lower level so that no regurgitation of bile and pancreatic juice into the thoracic segment of the esophagus occurred. The diaphragm is repaired by suture (fig. 12), and the patient usually im-

FIGURES 8–13.—Transthoracic esophagogastrectomy for cancer of gastric cardia. Figure 8, Intercostal incision in seventh interspace. Exposure obtained. Figure 9, Mobilization of esophagus and superior segment of stomach through radial incision in diaphragm. Figure 10, Application of De Petz sewing clamp distal to cancerous segment. Figure 11, Transection of stomach and esophagus and removal of tumor-bearing segment. Figure 12, Repair of diaphragm. Preparation for intrathoracic esophagogastric anastomosis. Figure 13, Completion of anastomosis.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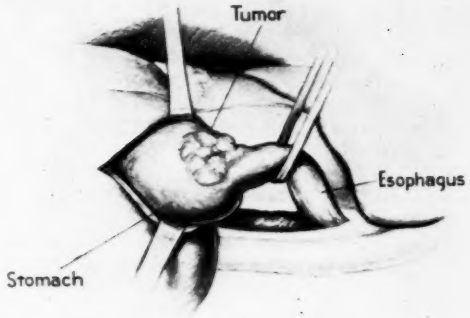
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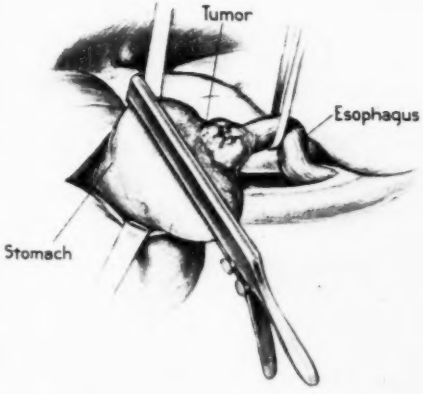
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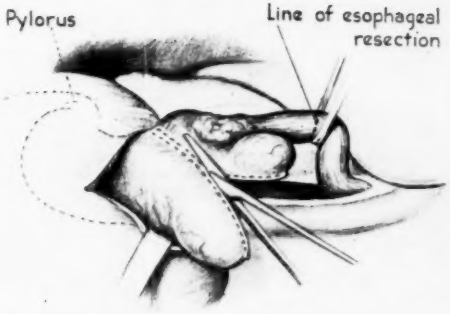
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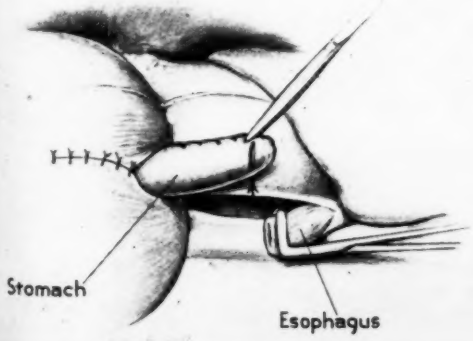
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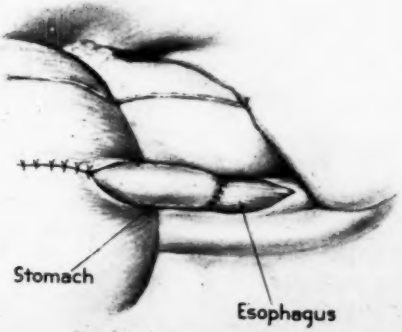
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mediately receives a high-caloric, high-protein diet by means of an orojejunal tube passed through the anastomosis into the jejunum. The exposure afforded by this technique is excellent, and the technical difficulties are not great. The operative mortality is in the neighborhood of 30 percent, but this figure can be explained by the fact that the operation is offered to aged patients, many of whom have cancers of the gastric cardia. In the Gastric Service at Memorial Hospital this operation has been performed on approximately 50 patients during the past 4 years. Some of the early patients are still living and free of evidences of recurrence. Another indication of improvement in the surgical treatment of gastric cancer may be appreciated when we state that the resectability of cancers of the gastric cardia in our experience has increased to 58 percent of the total number of patients subjected to laparotomy or thoracotomy.

CONCLUSIONS

Improvement in end results in treatment of gastric cancer may be attributed to a greater awareness on the part of the general public, improved facilities for the diagnosis of cancer, a wider application of surgical resection by an increased number of surgeons, who are performing the operations in numerous hospitals throughout the United States, and finally by the introduction of extremely radical surgical procedures, of three types, namely, removal of the organs adjacent to the stomach that are involved by contiguity with the cancer, total gastrectomy when the cancer involves the major part of the stomach, and transthoracic, transdiaphragmatic cardiectomy for cancers involving the gastric cardia.

Although the operative mortality for the major procedures is greater than for the simple subtotal gastrectomy, the number of total patients salvaged from those having the disease is inevitably increasing. Added to this are the advantages accruing from a better appreciation of proper preoperative and postoperative care of the patient and from a more widely disseminated knowledge of metabolic disorders coincident with and related to gastric cancer.

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AN ATTEMPT TO PRODUCE MALIGNANT TRANSFORMATION OF GASTRIC ULCERS IN RABBITS; A PRELIMINARY REPORT

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Whether peptic ulcers of the stomach may be the site of origin of malignant neoplasms is a mooted question. It is a question which probably cannot be answered with finality by clinical observations alone.

The investigation reported here represents an attempt to induce malignant neoplastic growth in an artificially produced defect of the mucosal lining of the stomach by the oral administration of a carcinogen. Two considerations prompted this undertaking: (1) It was felt that such an experiment might cast light upon the problem of the possible origin of cancer in peptic ulcers of the stomach; and (2) it was believed that this might represent a fruitful means of producing adenocarcinoma of the glandular portion of the stomach experimentally. Furthermore, it might provide some information regarding the effectiveness of exogenous carcinogens in inducing carcinoma of the stomach.

The rabbit was selected as the experimental animal in this study because it is the only common laboratory animal in which an artificially produced defect of the gastric mucosa leads to a chronic callous ulcer with papillomatous overgrowth of the mucosal edge. Our experience with this type of ulcer has shown that when the rabbit is permitted to consume its normal "rough" diet an ulcer produced by excision of the gastric mucosa will require several months to heal (*1*, *2*). It was felt that the chronicity of this type of ulcer would increase the opportunity for exposure to orally administered carcinogens while the tendency toward exuberance of the overgrowing mucosal edge would favor neoplasia.

MATERIALS AND METHODS

Six wild brown (Kansas cottontail) rabbits and ten domestic rabbits were used. The former initially weighed approximately 3 to 4 pounds, the latter between 5 and 12. All but two were females.

The wild rabbits became and remained emaciated. The domestic rabbits from time to time were afflicted with various diseases common to this species.

Carrots, green leafy vegetables, and dry alfalfa feed, or a commercial powdered pelleted feed comprised the diet.

Each animal received 15 mg. of 20-methylcholanthrene[1] per day orally. Various means were employed to get the methylcholanthrene into the stomach. Usually it was administered in a capsule with 0.1 cc. of benzene. Sometimes it was fed by hand on a lettuce leaf.

[1] Referred to as MCA hereinafter.

Under ether anesthesia, a midline abdominal incision was made, and a gastrotomy of the anterior wall of the pyloric portion was performed. After removal of the gastric contents the posterior wall of the stomach was exposed through the gastrotomy, and approximately 1 cm.^{2} of mucosa (down to the plane of cleavage in the submucosa) was removed by sharp dissection. The edge of the "ulcer" thus formed was oversewn with silk or linen thread in order to delay healing.

The stomachs of animals which were killed or which had died were opened along the greater curvature, washed with cold water, and fixed in 10 percent formalin. Serial histologic sections were prepared and stained with hematoxylin and eosin.

RESULTS

A summary of the length and type of treatment given each animal appears in table 1. Postoperative survival varied from 7 days to 13 months.

In the domestic rabbits the gross and microscopic findings were not remarkably different from those which we have observed in animals upon which the same surgical procedure was performed but which were not treated with MCA. In other words, there is no reason to believe that MCA altered the course of these lesions. The characteristic features of the surgical excision ulcer in the rabbit previously described (*1*, *2*) were evident. These included the typical undermined crater with hard, thick base and overhanging edges. Microscopically these features revealed themselves as dense fibrous scarring in the base and exuberant epithelial proliferation at the edge of the ulcer, which was much more marked in the domestic than the wild rabbits. In addition, the phenomenon of "epithelial inclusion" occurred. This refers to the complete isolation of an island of epithelium in the connective tissue at the edge of the ulcer (fig. 1). This, too, had been previously noted in animals not treated with MCA, and in our opinion is a normal part of the reparative process and is not to be considered as a neoplastic or invasive tendency, because these inclusions have never been observed to show invasive propensities. This point is of particular interest because these inclusions have been observed by others both in experimental animals (*3*) and in human material (*4*, *5*), and the opinion has been expressed that this is a malignant change.

In three of the four wild rabbits which received MCA for more than 1 month postoperatively, a change was noted which had never been encountered in rabbits not receiving MCA. This change consisted in the formation of glandular cysts in the base and edges of healing ulcers (fig. 2). These

FIGURE 1.—"Inclusion" of gastric mucosa about a healed gastric ulcer. Several authors have referred to this as indicating invasiveness. Such "inclusions" were found about a healed ulcer in practically every rabbit examined by us. × 50.

cysts were lined with a low cuboidal or flat epithelium. Perhaps the most interesting finding was the occurrence of multicellular layers in a portion of the wall of some of these cysts. At these points, there appeared to be breaking down of the basement membrane and growth outward into the surrounding connective tissue. However, great caution must be exercised in entertaining such an interpretation of these changes, and the possibility that these apparently proliferative regions of the cysts might be merely tangential sections of the cyst wall (fig. 3) must be borne in mind. Only further extension of the observation of these lesions can reveal their true nature. Twelve rabbits are under observation now and have been for from 9 to 18 months. We have never seen cystic changes in the mucosa of some 40 rabbits with "chronic" gastric ulcer. This causes us to consider the cystic changes to be of some significance; however, further controls are in progress.

No instance of neoplasm of the intestines has occurred in these animals in from 5 to 18 months. This is of interest because when MCA is fed to mice, various types of small intestinal tumors have resulted (*6*).

SUMMARY AND CONCLUSIONS

The daily oral administration of 15 mg. of 20-methylcholanthrene to rabbits in which a "chronic" gastric ulcer had been produced surgically has not resulted in any detectable change in the ulcer in domestic rabbits in from 3.5 to 5.5 months postoperatively. In similarly treated wild rabbits, formation of epithelial cysts occurred in three of the four animals autopsied after 5 to 13 months.

TABLE 1.—*Treatment given each rabbit*

Rabbit No.	Length of postoperative life	Condition of histologic specimen	Summary of treatment	Notes
Wild:				
A, B, C	1 wk. control	Fresh specimen		Normal mucosa.
1	1 mo. control	13-hr. post mortem		Do.
3	9 days control	15-hr. post mortem		Do.
2 [1]	7+ mos	11-hr. post mortem	5 mos. MCA in fat	Cystic mucosa.
6 [1]	5+ mos	Fresh specimen	do	Do.
8 [1]	do	Fresh specimen (but dehydrated).	do	Respiratory infection and cystic mucosa.
7	13 mos	Fresh specimen	5 mos. MCA in fat and 4 mos. MCA on lettuce	
Domestic:				
10	1¾ mos. control	5-hr. post mortem anterior wall.		Diarrhea, normal mucosa.
11	7 days control	Fresh specimen		Normal mucosa.
12	5½ mos	do	2½ mos. MCA in fat and 1 mo. MCA in benzene [2]	Do.
14	5 mos	2-hr. post mortem	1½ mos. MCA in fat and 1 mo. MCA in benzene [2]	Do.
13	do	20-hr. post mortem	do.[2]	Post-mortem changes.
18	do	Fresh specimen	do.[2]	Normal mucosa.
15	4½ mos	15-hr. post mortem	do.[2]	Do.
30	3½ mos	6-hr. post mortem	3½ mos. MCA in benzene and on lettuce [2]	Liver pathologic, diarrhea, normal mucosa.
20	5+ mos	No slides made	1½ mos. MCA in fat and 1 mo. MCA in benzene [2]	Normal mucosa.
23	4½ mos		4½ mos. MCA in benzene and on lettuce	Do.

[1] Cystic changes in the mucosa.

[2] After operation.

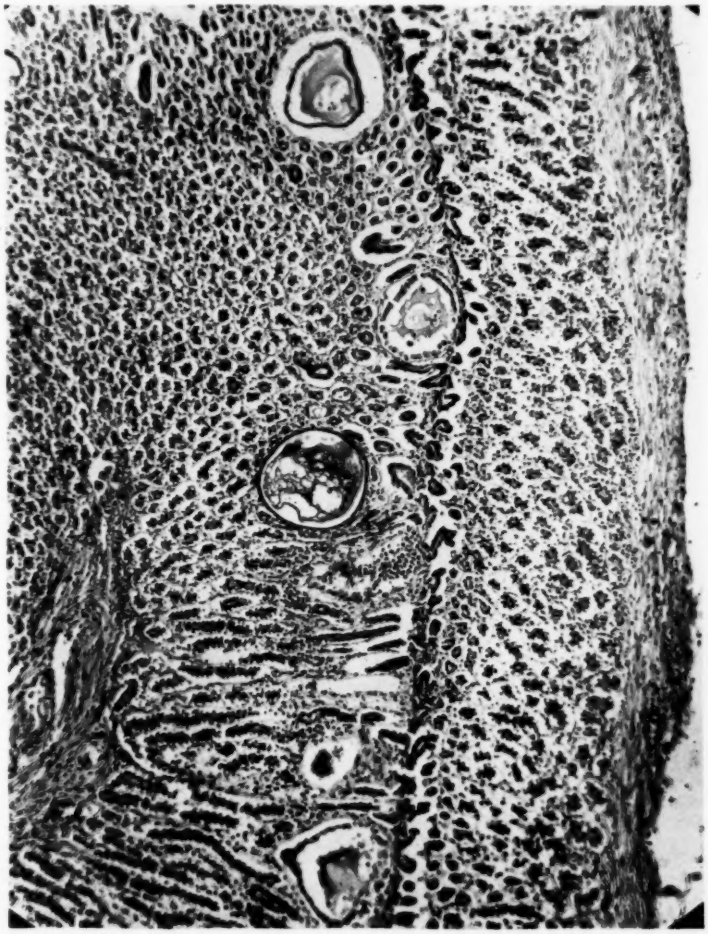

FIGURE 2.—Cystic changes in the gastric glands about a healed ulcer. × 85.

FIGURE 3.—Example of a change in a portion of the wall of a cyst which might be interpreted as invasiveness but which may only be the result of a tangential section. × 550.

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GASTRIC (AND SALIVARY) EXCRETION OF RADIOIODINE IN MAN (PRELIMINARY REPORT) [1]

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INTRODUCTION

In 1943 Davenport [3] called attention to the fact that several observers had reported that iodide in gastric juice is more concentrated than in plasma and that Lipschitz [4] had found that at low plasma-iodide concentration the concentration of iodide in gastric juice was as much as 15 times the concentration in plasma. Lipschitz also noted that as the plasma concentration rose the gastric concentration also rose but that the ratio of the gastric concentration to that in the plasma fell. In the same year, using dogs with Heidenhain or Pavlov pouches, Davenport verified the ability of the gastric mucosa to concentrate iodide. After injecting sodium iodide intravenously, he found that the iodide was recoverable as such and that there was no detectable molecular iodine, nondiffusible iodine, or organic iodine in the gastric juice. The concentration of the iodide in the gastric juice was independent of the rate of secretion. It was higher than the concentration in the plasma at plasma concentrations below 3 mM per liter and was equal to or lower than the plasma concentration at plasma concentrations above 3 mM per liter. He stated that iodide replaces chloride in the plasma and probably replaces chloride in the gastric juice. He could find no explanation of the mechanism of iodide secretion.

Since the stomach had been shown to be capable of concentrating iodide, we were interested to determine whether this concentrating power was altered in the presence of gastric disease, as we had found to be partially true in the case of sulfadiazine.[5] Instead of employing quantitative chemical methods for the determination of iodine, we decided to employ radioactive iodine as a "tracer" substance and to study its concentration in the saliva as well as in the gastric juice and blood, and in a few instances in the urine.

METHODS

The work on the gastric and salivary excretion of radioactive iodine as carried out in our laboratory divided itself into three periods according to the techniques employed, and the findings should be evaluated with this in mind. In the first period, radioiodine was obtained from the Massachusetts Institute of Technology,[6] and measurements were made with one or another of three Geiger-Mueller counters. Seventeen tests on fourteen patients were carried out by Dr. Henry S. Bloch and Leonard Cole.

In the second period, radioiodine from the Massachusetts Institute of Technology was still employed, but measurements were made with a single Geiger-Mueller tube (although three different scaling units were employed with it), and the geometrical relation of the samples to the tube was fixed.

Ten tests were carried out on ten patients. During this period the subjects or patients were given intravenously 0.25 to 0.5 millicurie of radioiodine in about 20 cc. of an aqueous solution containing 100 mg. of sodium iodide. The materials from these persons were tested for radioactivity by placing samples in bottle caps and counting with the equipment noted. The counts on any sample of material were compared only with counts on other material obtained from the same patient.

In the third period, the radioiodine used was obtained from Oak Ridge,[7] and measurements were made with a single Victoreen Geiger-Mueller tube and a single scaling unit with standardization every hour or two against a sample of radium D plus E [8] and against an aliquot of the radioiodine used for the injections. Twenty tests were performed on sixteen patients.

The methods used at present (third period) are carried out on persons who have fasted 12 hours. A Rehfuss tube is introduced into the stomach, and constant aspiration is maintained with a 50-cc. syringe. The subject or patient is instructed not to swallow any saliva but to spit into a beaker. Following collection of the basal gastric and salivary secretions (usually for 15 minutes), radioiodine and sodium iodide are given intravenously, 1 to 2 minutes being required for injection. Gastric juice and saliva are collected continuously for 120 minutes following the injection and divided into 10-minute samples. The character of the aspirated gastric juice is noted, and particular attention is given to the presence or absence of mucus, blood, or bile. Blood samples are taken from the

[1] Aided in part by grants from the National Cancer Institute, the Henry Meis Fund, and by a grant from the Jane Coffin Childs Memorial Fund for Medical Research.

[2] We wish to thank Dr. Harold Kersten, professor of biophysics, University of Cincinnati, for his advice and assistance. Technical assistance was given by Paul Gilson, Rev. John Schuler, Warren Stubbins, Sarah McCammon, and Margaret Naugel.

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[6] Kindly supplied through the courtesy of Prof. Robley Evans.

[7] Obtained through the courtesy of Dr. Paul C. Aebersold.

[8] Kindly supplied by Dr. L. F. Curtiss, National Bureau of Standards.

antecubital vein before the injection and at various intervals after injection. Urine is obtained from several patients by catheter, also in 10-minute intervals. Twenty-four-hour urine specimens are obtained several times to see at what rate the radioiodine is excreted.

The solution injected is made with sodium iodide and radioiodine solution. Radioiodine is received from Oak Ridge in aqueous solution in amounts of 30 millicuries in volumes of 20–30 cc. Before withdrawing the solution from the containers, 0.01–0.02 of a millimole of sodium iodide is added to decrease the loss of radioactivity in pipettes, syringes, etc. The glassware and needles used in the preparation and injection of the radioiodine solutions are kept separate and are used for this procedure only. They are checked for gross contamination with radioactivity by means of an electroscope. The radioiodine solution is measured into sterile sodium iodide solution with a sterile tuberculin syringe or a sterile 1- or 2-cc. pipette. When a pipette is used, aspiration is made with a syringe attached to it by rubber tubing. Radioiodine is given in amounts of 4 microcuries per kilogram of body weight, the suppliers' figures for the microcurie values being used and the decay of radioactivity calculated as occurring with an 8-day half life for the radioiodine. Sodium iodide is given in amounts of 0.01 of a millimole (1.5 mg.) of sodium iodide per kilogram of body weight. The sodium iodide solution is made by diluting the calculated volume of a solution containing 1.5 mg. of sodium iodide per 0.1 cc. with an equal volume of pyrogen-free distilled water, and boiling. The sodium iodide and radioiodine solutions are mixed and aspirated into a sterile 20-cc. syringe, and the mixture is then ready for injection.

The materials obtained from the subjects or patients are prepared for counting after measurements of volume and pH. All samples of saliva and gastric juice are made alkaline by adding 0.05–0.4 ml. of monoethanolamine and are heated to facilitate mixing and pipetting. Portions of the samples of 0.1–0.3 ml. are then measured onto microscope cover glasses and dried.

The dried materials are then ready for counting and are placed under a Victoreen Geiger-Mueller tube. This tube feeds an electrical pulse into a scaling unit every time an electron from a disintegrating atom enters the sensitive volume of the tube. The scaling unit with its attached recorder counts the number of these electrical pulsations. This count is corrected for resolving time and for background counts. The count thus corrected is compared with the count of the standard sample of radium D plus E. It is further corrected for the decay of radioactivity that occurs in the radioiodine standards, which are also counted as noted herein. Results are then expressed as percent of the radium D plus E count taken within an hour or two of the sample count. The counts are not corrected for absorption in sample material, which leaves the serum counts 10–20 percent too low. The other samples contained less solids than serum, and their counts are less in error from this source. The results are further converted into percent of the total injected dose recovered per liter of serum, gastric juice, etc., as the case may be.

Considerable difficulty has been encountered in obtaining satisfactory results with the equipment purchased for measurement of radioactivity. Two counting units consisting of Geiger-Mueller tubes, registers, Neher-Harper circuits, and scalers, serial Nos. 271 and 405, secured from the Cyclotron Specialties Co., as well as a third unit of similar design (modified Lifschutz circuit) built at the University of Cincinnati by Rev. John Schuler, under the direction of Dr. Harold Kersten, professor of biophysics, broke down repeatedly during the first two periods of counting. Except for the register and the Victoreen mica-window Geiger-Mueller tubes, the counting equipment at our disposal has been unsatisfactory for our purposes. With an extra amplification stage in the scaler input and replacement of various burned-out resistors, condensers, and faulty radio tubes, we have now obtained a counter which operates most of the time. Our previous experience was that with the three scaling units connected successively to the same Geiger-Mueller tube the ratio of the counts given by one scaling unit to those given by another scaling unit varied from sample to sample. Which of the various counts on a sample might be most suitable as a measure of its radioactivity was difficult to decide. We do not believe this difficulty has been overcome in the work presented here, which must be regarded with some circumspection on this account.

RESULTS

The results of this investigation are divided into three parts, according to the three techniques used as described. The first technique was employed in 17 tests on 14 patients; the findings showed concentration of 20 to 30 times as much radioactivity in the gastric juice and saliva as in serum following injection of radioiodine accompanied by small quantities (less than 1 gm.) of inert iodine. No differences were observed between persons with and without pathologic processes in the stomach. The second technique was employed in 10 tests on 10 patients, and the principal findings were similar to those previously reported. Results obtained by the second and third techniques are summarized in table 1. The third technique has been employed in 20 tests on 17 patients, the tests being numbered consecutively from the beginning of the second technique. In addition to the tabular summary,

TABLE 1.—*Concentration ratios of radioiodine*

NORMAL STOMACH

Study period	Test No.	Region involved	Diagnosis	Gastric juice / Serum	Saliva / Serum	Volume of saliva [1]	Volume of gastric juice [2]	pH of gastric juice	Character of gastric juice: Blood	Bile	Mucus
2	1			10–20	14–16	20	8–20	2	+	0	++
	2			15–20	15–35	7	5–10	2	+	0	+
	3			40–55	.....	1	2–10	4–6	0	0	+
	6			15–70	40–90	3	1–3	2–4	+	0	+
	7			4–18	.....	1	1–12	2–8	+	+	+
	8			20–50	20–60	6	2–10	2–4	+	0	+
	10			15–35	25–35	1	1–10	2–4	+	0	+
	24			25–30	65–80	.3	4–5	5–7	0	0	++
	26			10–25	40–130	1	1–10	5–8	0	++	+
	28			20–50	15–25	6	1–10	1–3	0	0	++

GASTRIC CANCER

2	4	Body		1–25	.....	.....	1–5	6	0	0	+
	5	Pylorus		15–60	.....	.....	1–10	6–8	0	+	+
3	17	Cardia		20–25	20–50	2	5–15	3–5	+++	0	+++
	14	Body		5–15	15–25	5	.....	3–5	++++	0	+++
	21	do		15–70	100–180	.8	1–10	3–5	0	0	+
	22	do		35–45	100–700	.4	2–10	3–7	+	0	++
	12	Pylorus		.1–1	10–20	2	1–10	4–5	+	?	+
	29	Pylorus (post operative).		5–25	20–200	.1	0–20	6–7	+	0	+
	20	Pylorus		35–45	40–300	3	5–20	3–7	0	0	+

MISCELLANEOUS GASTRIC TUMORS

3	11		Gastric leiomyoma (fundus)	15–20	15–20	4	2–10	3–6	0	0	++
	19		Gastic leiomyoma (fundus) (after excision of tumor).	15–30	15–30	4	1–10	7	0	0	+
	15		Gastric lymphoma (antrum)	15	15–30	.....	15–50	2–4	0	0	+
	27		Benign gastric polyp (body)	25–40	30–45	6	10–20	1–2	0	0	+

PEPTIC ULCER

2	9		Prepyloric ulcer	5–12	7–20	8	20–50	2–7	++	+	++
3	18		Gastric ulcer	10–15	10–30	14	15–30	1–2	0	0	+
	23		do	10–20	20–30	5	10–50	1–2	+	0	++
	30		Duodenal ulcer with vagotomy	20–45	30–50	4	5–20	1–3	0	0	++

MISCELLANEOUS

3	25		Diffuse atrophic gastritis	15–45	10–180	2	1–2	5–7	0	0	++++
	13		Carcinoma of ampulla of Vater (gastroenterostomy; hepatic metastases).	5–15	15–30	.....	20–30	2–3	0	++	+++

[1] Average cubic centimeters/10 minutes.
[2] Cubic centimeters/10 minutes.

the results of a number of the tests made with the third technique are presented graphically in figures 1 to 10 to illustrate in more detail the findings obtained.

Of particular interest are the results illustrated in figures 4, 5, 6, and 7. In test 12 (fig. 4) the concentration of radioiodine in the gastric juice was unusually low but was much higher when the test was repeated (fig. 5) following subtotal gastrectomy. We do not believe that the rise noted postoperatively can be explained by regurgitation of intestinal contents, since the specimens of gastric juice obtained contained no bile. We are unable to explain the differences noted. The results in figure 6 show that depression of iodine secretion in the gastric juice as shown in figure 4 cannot necessarily be explained by the presence of a prepyloric tumor. Figures 7 and 8 show a slightly higher concentration in both saliva and gastric juice after removal of a leiomyoma of the fundus. The significance of this difference is not known.

Table 1 summarizes our findings in 10 subjects without evidence of gastric disease. The concentration of radioiodine in the gastric juice was found to vary between 4 and 70 times the concentration in serum. The concentration of radioiodine in the saliva was found to be in general higher than that in the gastric juice. There was no relationship between the concentration of radioiodine in gastric juice and the pH of the gastric contents (compare tests 24 and 26 with the others).

Table 1 (second part) shows greater variation in the concentration of radioiodine in the gastric juice and saliva than is shown in table 1 (first

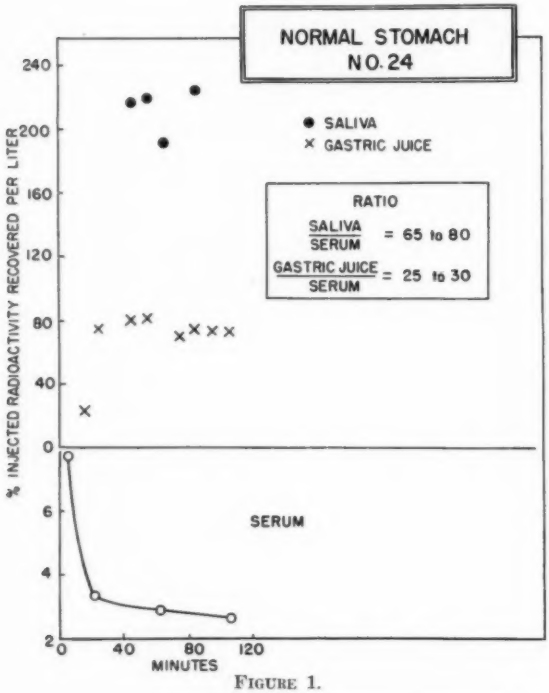


FIGURE 1.

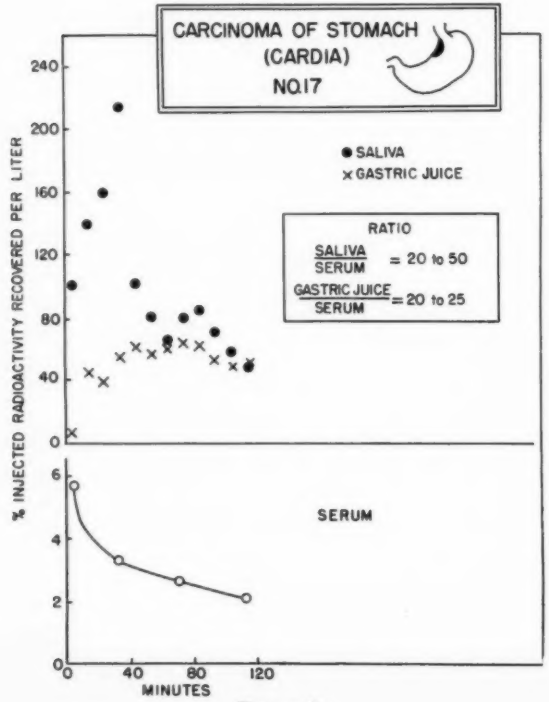


FIGURE 2.

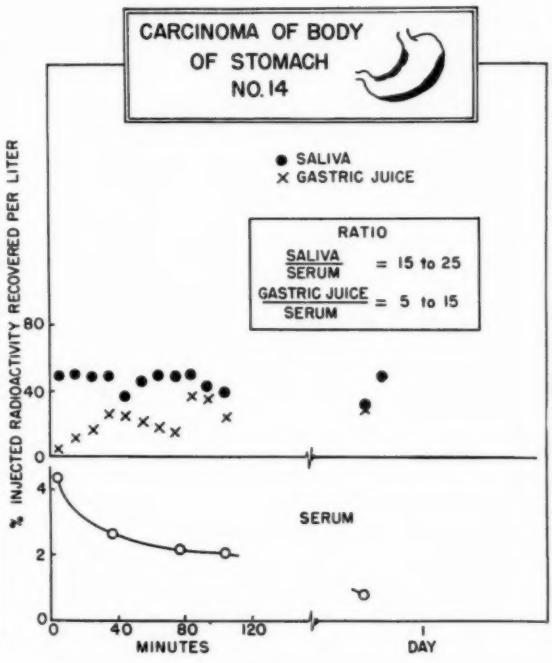
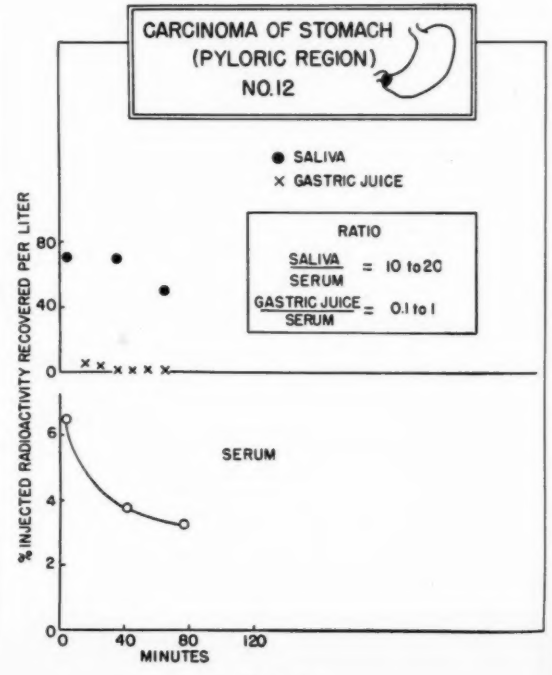


FIGURE 3.



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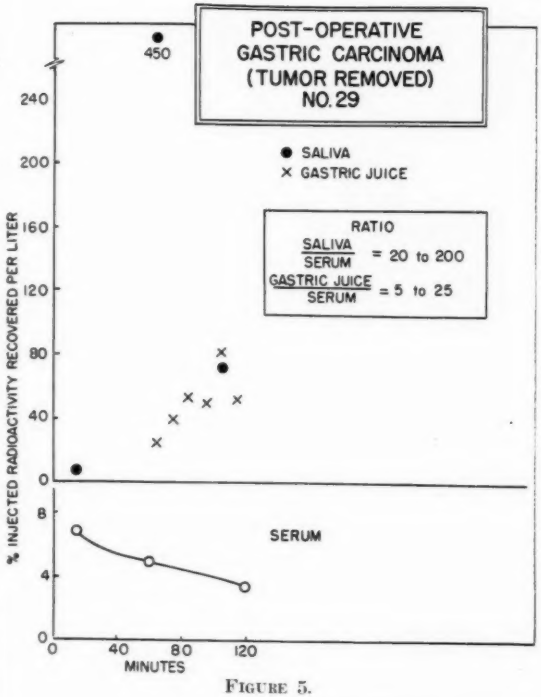

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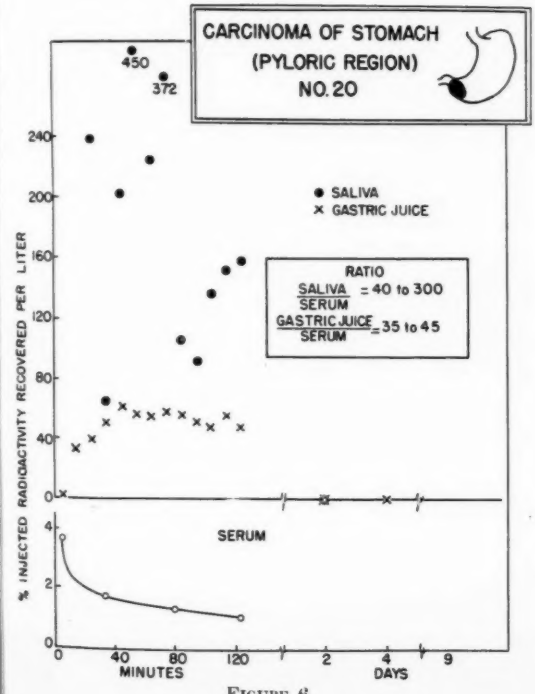

FIGURE 6.

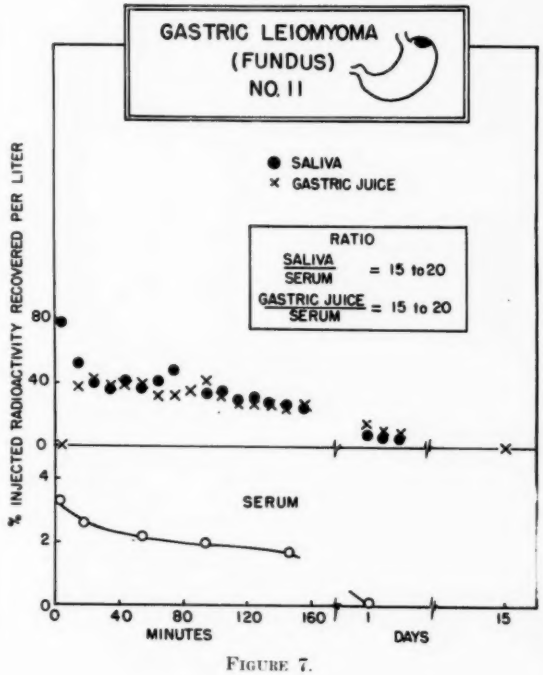

FIGURE 7.

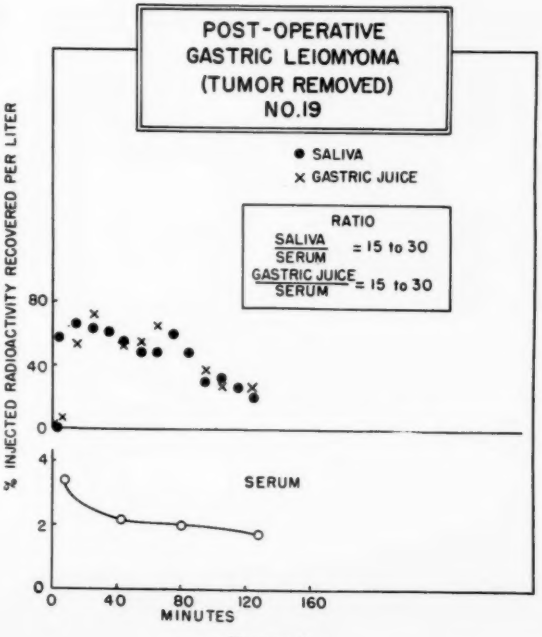

FIGURE 8.

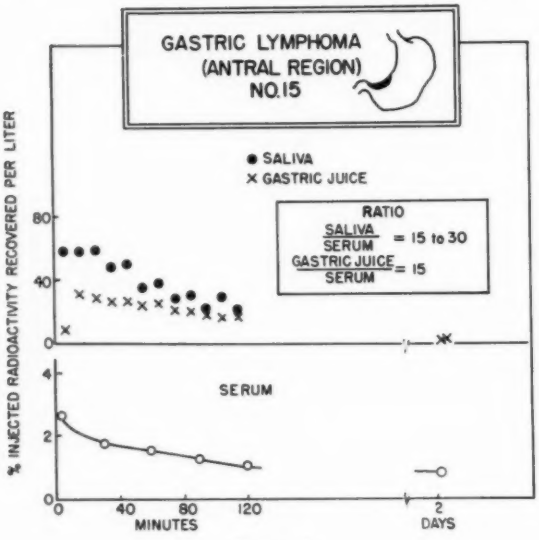

FIGURE 9.

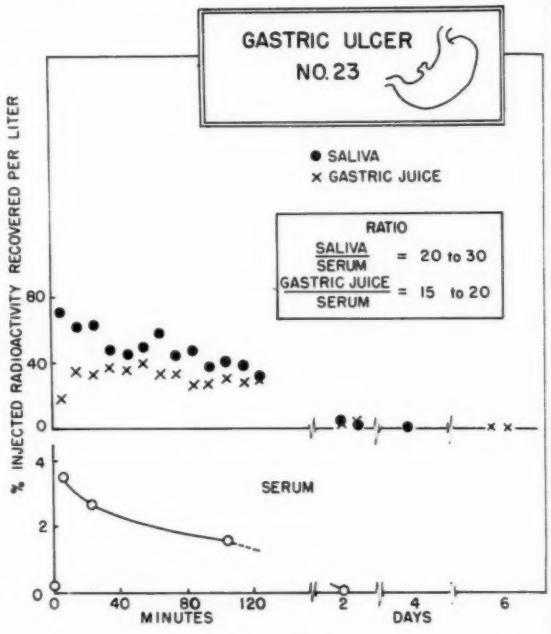

FIGURE 10.

part). We are unable to correlate the location of the tumor with the concentration of radioiodine in the gastric juice or saliva.

Table 1 (last three parts) illustrates the results obtained in patients with gastric tumors other than carcinoma, with peptic ulcer, and in one patient with diffuse atrophic gastritis and achlorhydria, and in a patient with duodenal ulcer, who had had a bilateral vagotomy 7 months before.

CONCLUSION

The stomach of man concentrates radioactive iodine to a considerable degree after the intravenous administration of 4 microcuries of radioiodine and 0.01 mM of sodium iodide per kilogram of body weight. No definite conclusions can be drawn as yet on the influence of gastric disease on the stomach's ability to concentrate radioiodine under the conditions of this investigation.

The salivary glands excrete the radioiodine usually in higher concentration than the stomach.

CONCENTRATION OF QUININE IN GASTROINTESTINAL CANCERS (PRELIMINARY REPORT) [1] [2]

By F. E. KELSEY, and A. BRUNSCHWIG, *Departments of Pharmacology and Surgery, The University of Chicago*

Quinine, in common with many other drugs, is selectively concentrated by several tissues of the body. The tissues in which the highest concentration is attained in vivo after oral or intravenous administration of quinine are pancreas, spleen, lung, liver, and kidney. Blood, muscle, connective tissue, and nervous tissue contain relatively little of the drug (*1–4*). Neither the mechanism of this concentration nor the cellular components responsible for it is understood. Several explanations have been suggested, including adsorption by the blood capillaries, by the cell membranes, or by cytoplasmic or nuclear colloids (*4, 5*). The selective staining of cell types and structures by certain dyes under specific conditions has long been used for histologic study of living and dead tissues; this specificity of staining is frequently due to a reaction between the dye and the tissue proteins. The in vivo localization of certain dyes in or around tumors has been described in animals (*6, 7*) and in man (*8*). An important question is, Are there metabolic differences between normal and neoplastic tissues which might serve as a basis for differential concentration of systemically administered compounds?

Once a drug specifically localized by neoplastic tissue is discovered, its inherent toxicity would be of relatively little importance, since the recent developments in the field of radioactive isotopes have made possible increases in the toxicity of any compound to any desired level by incorporation of such isotopes in the compound. In such instances, the nature of the toxicity is largely a matter of tissue localization of the drug. Accordingly, the need becomes obvious for a better understanding of the forces at play in determining tissue localization of drugs.

Quinine was selected for this study because of the availability of a sensitive and specific micromethod for its estimation in biologic samples and because its toxicity is sufficiently low to permit the use of relatively large doses. In addition, there are several reports in the literature suggesting the use of quinine and related compounds for the suppression of neoplastic growth (*9*). Some authors claim that beneficial effects, such as alleviation of pain, lessening of secretion, and even involution of tumors may result from quinine administration. Others have arrived at entirely negative results. In vitro, quinine alkaloids have long been known to exert a general poisoning action of protoplasm, and their inhibiting action on many enzyme systems is well-known. A growth inhibition of neoplastic cells was observed in tissue cultures when quinine or certain derivatives were added (*9*).

Quinine was given either by mouth or by vein and from 2 to 6 hours preoperatively. Blood samples were taken from 0.5 to 1.5 hours before and after tissues were removed. The quinine analyses were done by methods in use in this laboratory for 6 years (*10*). Total nitrogen values were obtained by a micro-Kjeldahl procedure; phospholipid and nucleic acid phosphorus analyses were done by the methods of Schneider (*11*). In all patients, the diagnosis of cancer was confirmed by histologic examinations. The data are given in table 1.

To date, 35 experiments have been done. These represent patients with a large variety of neoplasms, as well as several controls. In general, quinine was localized in cancer tissue to a greater extent than in the corresponding normal tissue. Data obtained on samples from typical patients with gastrointestinal cancers are given in the table. The degree of concentration is by no means great enough to be of any direct clinical significance, but the regularity with which it may be observed is suggestive of the existence of some component in neoplastic tissue which is present in higher concentrations or more probably is in a state of more active metabolism than in the corresponding normal tissue. In several instances, nitrogen and differential phosphorus analyses were done in order to show the relative amount of photoplasmic material being analyzed. There was no correlation between the values so obtained and the quinine concentrations observed. In vitro studies are being carried out and will be reported in detail elsewhere. In these studies, cell colloids are suspended in a cellophane bag and dialyzed against a saline-buffer solution containing quinine. In general, the extent of quinine adsorption by the cell colloids parallels that observed in vivo, but with some notable exceptions. Fractionation of the cell colloids resulted in the rather surprising observations that the albumins play an unimportant role and that isolated cell nuclei are no better adsorbents than is homogenized whole tissue.

The conclusion that quinine is selectively concentrated by neoplastic tissue seems to be justified. The extent of the concentration is too small to be of any immediate significance, but it is sufficiently large to encourage further work on the mechanism of fixation. Preliminary results with in vitro methods suggest that quinine is adsorbed on the nondialyzable constituents of the cell.

[1] Presented before the Gastric Cancer Conference December 5, 1946.

[2] This work was aided in part by a grant from the O. C. Miller Memorial Cancer Research Fund of the University of Chicago.

TABLE 1.—*Concentration of quinine in neoplastic and adjacent nonneoplastic tissues*

Patient No.	Diagnosis	Quinine in plasma, milligram/liter	Quinine as percent of plasma concentration in—			
			Muscularis	Mucosa	Carcinoma	Other
2	Carcinoma of the tongue	3.5	260	260	450	
33	Carcinoma of the esophagus	6.5	123	185	262	Lymph node, 370.
18	do	4.3	.....	232	312	
9	Carcinoma of the stomach	6.8	97	176	254	{Colon mucosa, 127. Colon muscle, 99.
27	do	3.4	.....	250	380	
29	do	8.7	.....	94	176	{Spleen, 207. Liver, 460.
3	Carcinoma of the colon	4.6	130	337	680	Anal skin, 310.
13	do	6.5	.....	121	191	Liver, 655.
20	do	4.6	146	382	663	Skin, 310.
30	do	6.2	65	200	134	Skin, 82.

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THE CYTOLOGY OF THE GASTRIC FLUID IN THE DIAGNOSIS OF CARCINOMA OF THE STOMACH[1,2]

By GEORGE N. PAPANICOLAOU, M. D. and Ph. D., and WILLIAM A. COOPER, M. D., *Lewis Cass Ledyard, Jr., Fellow, Cornell University Medical College and the New York Hospital*

INTRODUCTION

For some years we have been investigating, in our laboratory at Cornell Medical College, the problem of diagnosing cancer through the recovery and identification of exfoliated neoplastic cells. A technique has been developed which was first applied in the vaginal and uterine secretions for the diagnosis of cancer of the female genital tract.[3] Later on the work was extended to the examination of other fluids, such as urine, sputum, pleural and peritoneal exudates, and recently to the gastric secretion.[4] This report deals exclusively with the results of our studies on the diagnosis of cancer of the stomach by this cytologic technique.

The idea of examining the cellular elements of gastric fluid for the purpose of recovering cancer cells is not new. Similar investigations have been conducted in the past, but most efforts have been largely frustrated because of the rapid cellular disintegration, which usually occurs in the gastric fluid. We were gratified, therefore, to find that good preservation of the exfoliated cells and of their structural details could be obtained with an appropriate technique. While degeneration of cells is more of a problem in gastric secretion than in vaginal, pulmonary, or urinary secretions, with proper handling it is thought not to be an insurmountable problem.

This study was conducted as a joint venture in the Department of Anatomy at Cornell Medical College and in the Department of Surgery at the New York Hospital. The clinicians in the hospital submitted specimens to the laboratory without accompanying clinical information, and in most instances the reports were filed on the wards before the clinical diagnosis was established. All the patients were hospital cases, and most of them were suspected by the clinicians of having gastric cancer. In most instances the final diagnosis was confirmed by operation, biopsy, other clinical studies, or by the passage of time.

TECHNIQUE

The specimens were obtained by emptying the fasting stomach, with an ordinary Levine tube, of whatever secretions it had accumulated. An equal volume of 95 percent alcohol[5] was immediately added to the aspirated specimen, and this was sent to the laboratory. The method of handling these specimens is as follows:

(1) Mix gastric fluid as soon as obtained with an equal amount of 95 percent alcohol.
(2) Centrifuge without delay for 20 minutes at medium speed.
(3) Pour off supernatant fluid. Prepare smears from sediment. (If smears cannot be prepared immediately, cover sediment with 95 percent alcohol.)
(4) Spread sediment evenly on slides coated with film of Mayer's albumen.
(5) When edge of smear begins to show dryness, immerse slides in mixture of equal parts of 95 percent alcohol and ether.
(6) Fix slides in alcohol-ether mixture for 20 minutes or longer.
(7) Smears may be left in this mixture until ready to stain.
(8) Stain by methods described in footnote 8.

It should be emphasized that the immediate addition of alcohol to the gastric contents, early centrifuging of the specimen, and prompt fixation of the smears in alcohol-ether are important features for obtaining good fixation of the cells.

The staining technique is similar to that used in vaginal and other smears. It consists in staining the smears first with hematoxylin and then with the two counterstains described by Papanicolaou[6] as OG 6 and EA 36.[7] This last stain can be used full strength or diluted with equal parts of 95 percent alcohol. The diluted stain has the advantage of being more transparent.[8]

In certain cases, it is found that very satisfactory material with good preservation of the cells is obtained by simple gastric aspiration. In other cases, many of the cells obtained by simple aspiration are found to be poorly preserved. We are unable to make a conclusive statement regarding the optimum technique of obtaining gastric specimens. In some cases, gastric lavage yields material that is better preserved, and it may be advisable to have both aspirated and lavaged specimens in certain cases.

[1] This work was supported by the Commonwealth Fund of New York.
[2] Presented at the Conference on Gastric Cancer, held in Chicago on December 5, 1946, under the auspices of the National Advisory Cancer Council, U. S. Public Health Service.
[3] PAPANICOLAOU, G. N., and TRAUT, H. F.: Diagnosis of uterine cancer by the vaginal smear. 46 pp. The Commonwealth Fund, New York (1943).
[4] PAPANICOLAOU, G. N.: Diagnostic value of exfoliated cells from cancerous tissues. J. A. M. A. 131: 372–378 (1946).
[5] If 95 percent alcohol is not available, isopropyl alcohol, denatured ethanol, or pure methanol may be used as a substitute.
[6] PAPANICOLAOU, G. N.: New procedure for staining vaginal smears. Science 95: 438–439 (1942).
[7] A stain corresponding to EA 36 is marketed by the Ortho Pharmaceutical Corporation as EA 50.
[8] Staining procedure is as follows: After fixation in alcohol-ether, the smears are washed in 80, 70, and 50 percent alcohols and distilled water; stained in Harris hematoxylin diluted with an equal amount of distilled water for 2 to 4 minutes; washed in distilled water, and then in running tap water for 10 minutes; rinsed in distilled water, and run up through 50, 70, 80, and 95 percent alcohols; stained in OG 6 for ½ minute; washed in 95 percent alcohol (two changes); stained in EA 36 for 1 minute (full strength or diluted); washed in 95 percent alcohol (three changes), dehydrated in absolute alcohol, cleared in xylol, and mounted with cover slips.

Among the possibilities to be explored in this regard are lavage with diluted alcohol, which has yielded some very well preserved specimens, and the use of other materials to produce gastric exfoliation. One should, of course, avoid the use of any substances that might injure the gastric mucosa.

Recently we obtained some excellent specimens by continuous aspiration for 15 minutes without lavage.

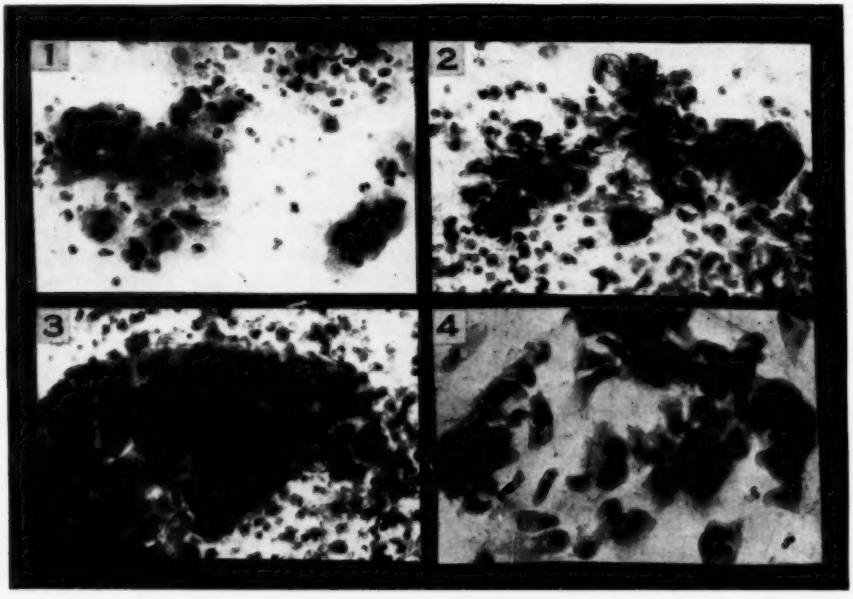
CYTOLOGY OF NORMAL STOMACH SECRETIONS AND CRITERIA FOR MALIGNANT CELLS

The cytology of the gastric fluid is unique in that many of the cells are derived from other organs. Squamous cells of the esophageal or oral mucosa are usually found in the gastric fluid, sometimes in large numbers. Cells exfoliated from the respiratory epithelium are also frequently carried into the stomach by the swallowing of bronchial discharge. When the Levine tube is introduced through the nose, cells or even patches of the nasal mucosa may be carried into the stomach. Such extraneous cells or cell groups may lead to an erroneous interpretation, though as a rule their nature and origin can be recognized. Ciliated cells can be identified by their cilia or their heavy cuticular membrane, histiocytic cells of the respiratory tract by their inclusions of foreign particles.

Normal cells of the gastric mucosa are of the columnar mucoid type and appear singly or in clusters. They are usually inconspicuous or totally absent and only rarely appear in large numbers. They may be numerous when a superficial lesion of the mucosa is present. Parietal and chief cells of the gastric glands are rare and difficult to identify unless they are grouped. In one instance of a deep gastric ulcer, some smooth muscle fibers were found. Because of the pronounced cytolysis, stripped nuclei are common. Leukocytes, histiocytes, plasma cells, and erythrocytes are found in varying numbers. Plasma cells usually indicate a chronic inflammatory process but are often found in carcinomas, occasionally in large numbers.

The identification of cancer cells is facilitated by their abnormal traits, the most characteristic of which involve the nuclei. These are nuclear enlargement out of proportion to the size of the cells, mitotic activation, unequal fragmentation, hyperchromatia, and large and atypical nucleoli. The form and size of the cancer cells and the structure of their cytoplasm show considerable variation depending upon their type and origin. In adenocarcinomas, the cells are more rounded and resemble adenocarcinoma cells from other organs (figs. 1–3). In mucous carcinomas, one finds many columnar forms, in which the presence of mucin can be demonstrated (fig. 4).

Cancer cells may appear singly or in clusters. Although single cells are often pathognomonic, a positive diagnosis should be based as much as possible on clusters, which offer additional criteria.



FIGURES 1–4.—1–3, Adenocarcinomas of the stomach; 4, Mucous-cell carcinoma of the stomach. × 285.

such as crowding, irregularity of pattern, anisocytosis and anisonucleosis, engulfment, and lack of definition in cell boundaries.

METHOD OF REPORTING

The specimens are reported as negative, suspicious, or positive in one of five classes. The evaluation of each of the five classes of reports is given in the following tabulation:

Class 1, absence of normal or atypical cells;
Class 2, atypical cells present but without abnormal features;
Class 3, cells with abnormal features but not sufficiently pathognomonic;
Class 4, fair number of pathognomonic cells and cell clusters;
Class 5, large number of conclusive cells and cell clusters.

Classes 1 and 2 are essentially negative reports; class 3 is definitely suspicious, but not positive; and classes 4 and 5 are positive. In reporting the cases, we have tended to be conservative, classes 4 and 5 being reserved for those cases in which there was little doubt of the presence of abnormal cells.

CLINICAL CORRELATION

So far 137 cases have been studied by this method. The accuracy of the reports is shown in table 1.

Many of the cases suspected by the clinician of having gastric cancer turned out to have other diseases. Someone once said that clinicians can be divided into two groups: (1) Those who are eternally suspicious of gastric cancer and never find it; and (2) those who never suspect gastric cancer yet always miss it. It would appear that the doctors at the hospital fall into the first group.

TABLE 1.—*Accuracy of reports on gastric smears*

Interpretation of reports, final diagnosis	Cases	Class					
		1	2	3		4	5
		Negative		Suspicious		Positive	
		Number	Percent	Number	Percent	Number	Percent
Cancer	27	10	9.01	7	43.75	10	100
Not cancer	110	101	90.99	9	56.25	0	.....
Total	137	111	.....	16	.....	10	.....

The clinical correlation in the 137 cases is shown in table 2. Of the 27 cases having cancer, there were 10 false negatives, 7 suspicious, and 10 positive diagnoses. Three of the ten cases that were missed proved to have scirrhous cancers. There seems little hope for the accuracy of this method in this type of tumor, for desquamated cells are likely to be scanty or totally absent. In 3 other cases that were missed, the cells were poorly preserved in the only specimens received in the laboratory. As we have gained experience with this method, we have learned to be cautious about reporting specimens in which the cellular elements are degenerated. It might be wise to discard these specimens entirely. In the other 4 cases that were missed, there is no alibi except that but 1 specimen was examined in each case. Just as the clinician may wish to palpate an elusive mass a second or third time, it is advantageous to examine more than 1 specimen, especially if the first specimen is poorly preserved. In the suspicious cases particularly, at least 3 well-preserved specimens should be examined before arriving at a conclusion.

In the seven cancer cases reported as suspicious, one proved to be a lymphosarcoma, and in two others we had but one specimen. In five of the seven cases, we had two specimens.

TABLE 2.—*Analysis of cases included in table 1*

Interpretation of reports	Cases	Class					
		1	2	3		4	5
		Negative		Suspicious		Positive	
		Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Gastric cancer	27	10	37.03	7	25.94	10	37.03
Total not ulcer	110	101	91.81	9	8.19	0	.....
Gastric ulcer	26	24	.....	2	.....	0	.....
Duodenal ulcer	26	23	.....	3	.....	0	.....
Other diseases	58	54	.....	4	.....	0	.....

In the 10 cases reported correctly as definitely positive, 2 are of particular interest. One was a lesion of the cardia of which there were 2 negative X-ray reports. The other was reported as a gastric ulcer by X-ray, at the operating table, and by gross pathology. Only on microscopic study was a small cancer seen in one quadrant of the ulcer.

The correlation in the cases not having gastric cancer was high. In the 110 cases there were no false positive reports, and 9 class 3, or suspicious reports. Among the 9 false suspicious reports was 1 of a patient who proved to have cancer of the pancreas, and in 3 cases only 1 poorly preserved specimen was examined.

We wish to emphasize the preliminary nature of this work. There are many technical problems that remain to be studied. It is hoped that by improved handling of the specimens and by more vigorous application of the method, its accuracy and usefulness in clinical cases suspected of having gastric cancer will be increased.

Chairman Brunschwig: Dr. Spencer, did you wish to make a motion?

Dr. R. R. Spencer (Chief, National Cancer Institute): Mr. Chairman, I wish to move that this conference authorize Dr. Brunschwig, as chairman, to send the following telegram to Dr. George M. Smith, New Haven, Conn.:

Third gastric cancer conference now in session at University of Chicago voted that I express to you appreciation of your untiring efforts which have made this meeting possible. We deeply regret your unavoidable absence.

The motion was unanimously carried. The meeting recessed at 1 o'clock.

THURSDAY AFTERNOON SESSION

DECEMBER 5, 1946

The meeting convened at 2 o'clock, Dr. Andrew C. Ivy, of the University of Illinois, presiding. The following papers were presented, without discussion:

Experimental Impairment of the Gastric Mucous Barrier in Dogs, by Dr. Franklin Hollander, B. P. Sonnenblick, and Herbert A. Sober, Mount Sinai Hospital, New York City.

New Technique for Studying the Cytology of Gastric Aspirates in Man, by Dr. Franklin Hollander, Manfred Hess, and Herbert A. Sober, Mount Sinai Hospital, New York City.

Gastric Acidity Before and After the Development of Carcinoma of the Stomach, by Drs. Mandred W. Comfort, Mavis P. Kelsey, and Joseph Berkson, Mayo Clinic.

The Role of Cancer-Prevention Clinics in the Detection of Early Gastric Cancer, by Dr. Morris E. Dailey, University of California.

An Attempt to Identify Likely Precursors of Gastric Cancer, by Drs. David State, Richard L. Varco, and Owen H. Wangensteen, University of Minnesota.

Gastric Carcinoma: Can an Increased Diagnostic Accuracy Greatly Improve Survival Rates, by Dr. Frederic E. Templeton, Seattle.

Biologic Characteristics of Nonpalpable, Nonsymptomatic, Solitary Polyps of the Rectum, by Dr. Marie Ortmayer, Women and Children's Hospital, Chicago.

EXPERIMENTAL IMPAIRMENT OF THE GASTRIC MUCOUS BARRIER IN DOGS[1]

By FRANKLIN HOLLANDER, B. P. SONNENBLICK, and HERBERT A. SOBER, *Gastroenterology Research Laboratory, The Mount Sinai Hospital, New York City*

In a review of the possible relations of gastric physiology to gastric cancer, presented at the last meeting of this conference, Ivy (*1*) discussed several aspects of the problem which merited exploration. Chief among these was the entire subject of mucus secretion in the stomach, to which little attention had so far been given. In the report from this laboratory presented at the same time, it was emphasized that mucus collected from gastric pouches in dogs usually contains cellular material in addition to the extracellular secretion (*1, pp. 330–331; 2*). The gross correlation between intensity of exfoliation and irritant power of the stimulus (*3*) indicates that desquamation of mucous cells, like the secretory response itself, is a definitive response to even the mildest forms of irritation. The major function of mucus is to protect the glandular epithelium of the gastric wall. Hence, desquamation constitutes an auxiliary protective device, and for this reason we extended the concept of the "mucous barrier" of the stomach to include the mucous cell as well as the secretion per se.

The existence of the mucous barrier may serve to explain the failure to induce malignant tumors in the glandular portion of the stomach, following oral administration or direct application of carcinogens (*4*). It is our purpose today to describe a series of experiments with Heidenhain-pouch dogs in which the mucous barrier has been damaged, and its subsequent recovery investigated. With the knowledge thus obtained, we shall be in a position to determine whether such experimental carcinogenesis, which has not been possible in the presence of a normal mucous barrier, is possible after it has been impaired.

The entire study on any one dog consists of a set of three experiments, arranged in the following sequence: (1) A preliminary period to establish the absence of free acidity (½–1 hour), followed by the fatigue experiment proper, consisting of six or seven cycles of stimulation and collection of mucus (18–21 hours); (2) the first recovery period (30–36 hours), followed by the first follow-up experiment, usually of two cycles of stimulation and collection (6 hours); (3) the second recovery period (3–5 months), followed by the second follow-up experiment of three or four cycles (9–12 hours).

Mucus secretion is stimulated by the application of 5 percent eugenol-water emulsion to the pouch mucosa of a fasting dog. Each cycle of stimulation and collection of mucus, designated A, B, C, etc., involves the following steps: (1) Stimulation for 15 minutes and removal of the stimulus; (2) continuous drainage of four successive 30-minute samples; and (3) an interval of rest for 15 to 30 minutes, before starting the next cycle. In the fatigue experiments, stimulation was repeated as many times as was required to effect an alteration in the character of the secretion which persisted for at least two cycles. The number of cycles in the follow-up experiments was determined by the time required to attain essentially the same end point. The samples were studied from two different aspects: (1) Physicochemical; and (2) cytologic. The following characteristics of the samples included in these two categories were studied quantitatively, either by physical methods or on an arbitrary scale of 4 degrees.

The physicochemical characteristics were (1) volume of sample, (2) electrometric pH, (3) opacity, (4) viscosity, (5) percent solids, (6) specific gravity, and (7) intensity of blood color.

The microscopical characteristics were (1) intracellular and extracellular "mucin," i. e., metachromatic material; (2) columnar cells, whether single, in ranks, or in clumps; (3) neck chief cells; (4) parietal cells; and (5) leukocytes and fibrin.

The three experiments on any one animal, i. e., the fatigue experiment and the 2 follow-up experiments, entailed the collection and study of about 60 samples. Two to six smears were prepared from each sample and strained with toluidine blue. Up to this time, such experiments have been performed on 4 dogs, 2 of which have already been carried through the second follow-up experiment. For analysis of the observations on any one animal, the data are charted sample by sample in a series of bar graphs (figs. 1 and 2). Each graph represents a single variable and illustrates the relations among the sample within any one cycle. Then, in order to correlate the changes in the various characteristics, cycle by cycle, the data for the samples within any one cycle are averaged, and plotted as line graphs (fig. 3).

These graphs follow a pattern, which is essentially the same for all four dogs. Within any one cycle of the fatigue experiments proper (fig. 1), volume, opacity, percent solids, and viscosity all decrease toward the end of the cycle, whereas pH and blood tend to rise. Mucin and columnar cells also tend to fall off during the latter part of the cycle. The first appearance of neck chief cells and leukocytes usually does not occur until the second half of the cycle (fig. 2). Turning to the summary graphs (fig. 3), we find a striking amount of agreement among the variables, in regard to the

[1] This investigation is being conducted with the aid of a grant from the National Cancer Institute.

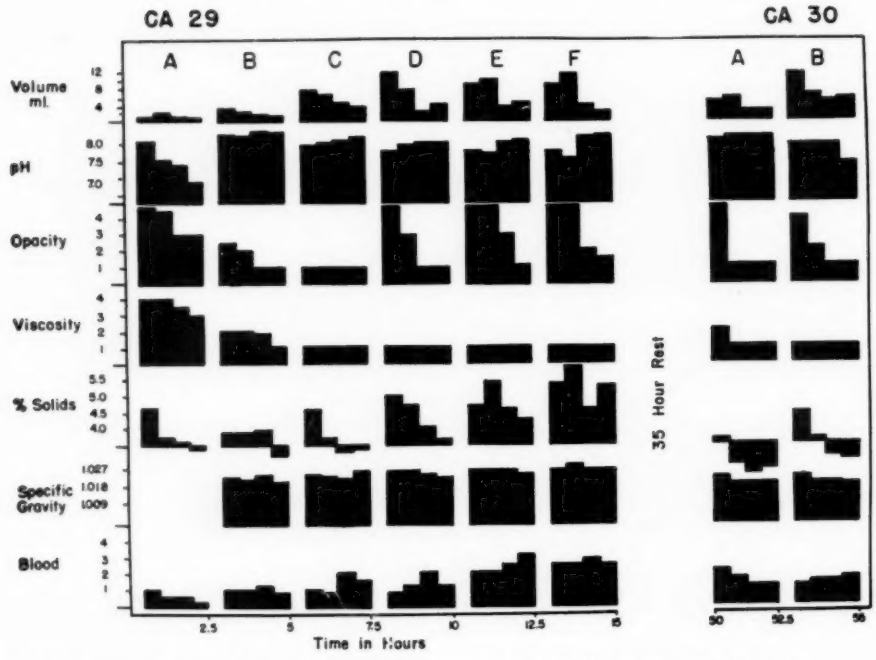


FIGURE 1.—Mucus fatigue experiment, physical and chemical characteristics. Dog No. 171.

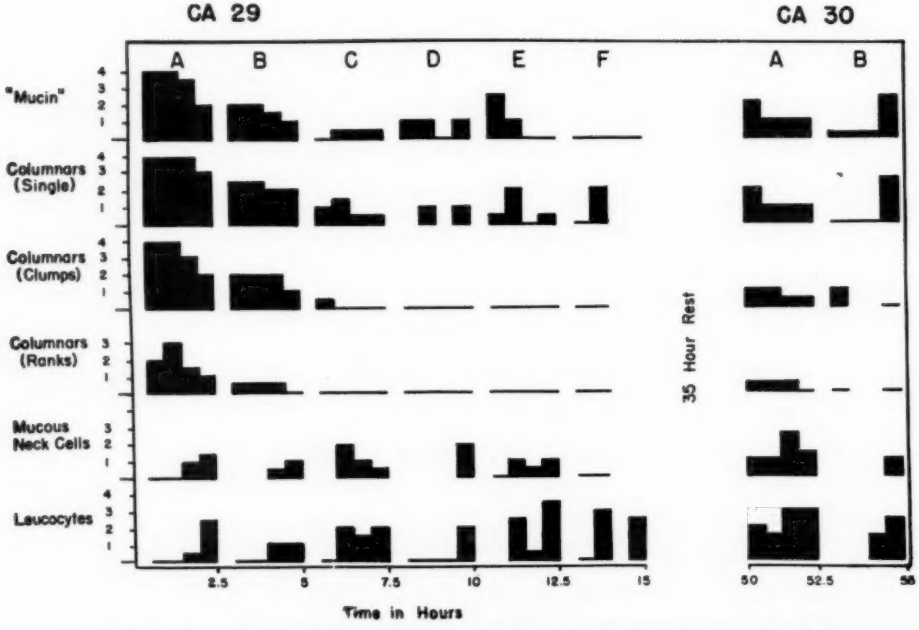


FIGURE 2.—Mucus fatigue experiment, cytologic charactertistics. Dog. No. 171.

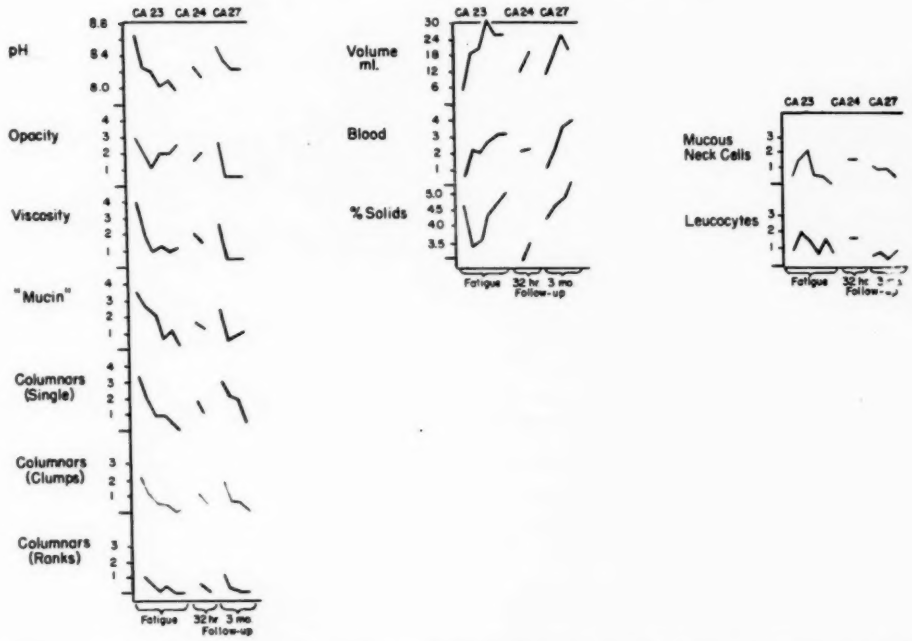


FIGURE 3.—Summary of mucus fatigue experiment, including follow-up after 32 hours and 3 months. Dog No. 175.

over-all trend and its time relations. For convenience, all variables which follow the same general pattern are grouped in one vertical column. The curves for pH, opacity, viscosity, mucin, and columnar cells all decrease sharply until the middle of the experiment; thereafter they level off with the exception of opacity, which increases. Volume, blood, and percent solids, on the contrary, show a general tendency to increase with successive stimulations. The curves for neck chief cells and leukocytes show no definite relation to those for the other variables. For the dog of the illustrative experiment, all the curves in the first column show a change in direction after the third cycle. The data for the other dogs manifest this change also, either in the third or the fourth cycle. The consistency of this behavior is noteworthy and indicates significant alterations in the character of the secretion at this time.

Well-preserved parietal cells, both mononucleate and binucleate, appear occasionally; no attempt was made to estimate their incidence because of their paucity. Peptic cells have not as yet been observed.

Thus, at the beginning of the fatigue experiment, the specimens consist of a relatively small volume of an opaque, jellylike material, with high pH and great density of columnar cells containing intracellular mucin, in short, typical mucus. About the middle of the experiment, the volumes are at least five times as large; the material is a decidedly pink fluid, free-flowing, tenacious, transparent or translucent, and of lower pH and epithelial-cell content. Some extracellular mucin is still present but in greatly diminished amount. By the last cycle, the volume is still high, and the resemblance to typical mucus is lost completely; the specimens are deep red and contain fibrin and leukocytes but few other cellular elements. The material is now chiefly inflammatory exudate. Hence, as a result of repeated irritation of the gastric mucosa, not only has the mucus-secreting apparatus been fatigued, but also the mucous barrier has been seriously damaged.

In the first follow-up experiment, 30–36 hours later, the response of the pouch mucosa to renewed irritation is radically different from that at the beginning of the fatigue experiment. This is true for all the variables and for every dog studied. The first cycle now approximates a condition intermediate between those in the second and third cycles of the initial experiment and indicates that recovery to the original state is incomplete. Further evidence of this difference in the integrity of the mucosa is evidenced by the cytologic picture. In addition to the small ranks and palisades of high columnar cells encountered in the beginning of the fatigue experiments, considerably larger tissue fragments are found in the samples of this follow-up. These particles, often comprising sev-

eral hundred cells, include not only high columnar cells but also smaller, more cuboidal elements with central nuclei. The cellular picture in these aggregates is suggestive of the transitional cells which lie between the free surface of the mucosa and the base of the crypts.

The second follow-up experiment, 3–5 months later, indicates that recovery is still incomplete. The response to renewed insult is essentially the same in the first cycle of this experiment proper, except that numerous large fragments of tissue now are noted, especially in the early part of the cycle, whereas they are found but rarely in the fatigue experiment. The second cycle is comparable with the third or fourth of the original experiment; the third cycle of the follow-up, however, consists almost completely of inflammatory exudate, which was obtained, in the fatigue experiment itself, only by the fifth or later cycles. In short, 3–5 months after the initial injury to the tissue, the mucosa is more friable and is fatigued more readily than it was originally.

What are the implications of these findings with reference to experimental carcinogenesis in the glandular stomach? Ivy (*1*) has said:

> If a chronic gastritis could be produced in an animal or if the mucus barrier could be destroyed, adenocarcinoma of the stomach might be produced by the oral administration of a carcinogen.

We have shown that, by repeated application of a eugenol-water emulsion, at least parts of the mucosa have been progressively denuded of mucus secretion, of the protective layer of columnar cells, and even of many of the neck chief cells. By the fourth application, the mucous barrier has been seriously impaired, and the disturbance has persisted for at least 3 months. Following the sixth application, there is evidence of a considerable inflammatory reaction of the tissue, and this has been confirmed by endoscopic observation of two of the pouches. The extent and chronicity of the inflammation is being investigated by means of biopsy specimens, and later also by experiments necessitating killing of the animals. Comparable investigations will be performed on rats, in order to determine the amount of irritation required to damage the glandular mucosa, as well as the nature of the response in the rodent. The possibility that mucous secretion and mucous cells constitute the barrier to experimental induction of an adenocarcinoma of the glandular stomach will then be tested, following the impairment of this protective mechanism.

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NEW TECHNIQUE FOR STUDYING THE CYTOLOGY OF GASTRIC ASPIRATES IN MAN[1]

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It is essential that the physiology of mucus secretion in man be studied systematically. Our previous paper (*1*) discussed an investigation into the impairment of the mucous barrier in dogs, including the attendant desquamation. If the response of the human stomach to mild irritation is analogous to that of the dog, then the introduction of an irritant into the gastric cavity of man should similarly induce greater quantities of desquamated epithelium than can be aspirated from the unstimulated, fasting stomach. Hence, it became necessary to devise a procedure for studying human subjects, in place of the pouch technique used for animals. The present report is a discussion of such a procedure, based on the collection of gastric aspirates following suitable stimulation of the mucosa, and the cytologic study of smears prepared from them.

In the course of developing the technique, a number of possibilities were explored. As the stimulus, water saturated with ether was tried and discarded because of the attendant discomfort. An emulsion of eugenol in water was tried in various concentrations; 1 percent produced inadequate quantities of secretion; 5 percent was excessively irritating to the mucosa; but 2 percent had neither of these objections. Fifty to three hundred cubic centimeters was employed, and 200 cc. was found to be the optimal amount. Fifteen minutes of stimulation was adopted because shorter intervals afforded insufficient amounts of material. No more than four 15-minute samples of mucus, withdrawn in succession, were required for our purposes. The volume of aspirated material varied considerably and was usually largest in the first or second collection.

The procedure finally evolved for collecting mucus from fasting human subjects entails the following steps: A Rehfuss tube is passed in the usual way and the stomach emptied by aspiration. Then at least one 15-minute sample of resting secretion is removed in order to study the "spontaneous" gastric secretion. Following this, 200 cc. of a 2-percent eugenol-water suspension is introduced through the stomach tube as rapidly as possible without causing distress. The subject is then placed in a reclining position for 15 minutes, during which he is turned from right side to left, and then on his abdomen, to insure maximal area of contact between stimulus and mucosa. The stimulating fluid is aspirated as completely as possible, after which four successive aspirations of gastric contents are performed at 15-minute intervals. Smears are prepared from each sample immediately after withdrawal and air-dried without other fixation. The remainder of each sample is then examined for the physicochemical characteristics investigated in the dog experiments.

For this preliminary work, subjects were chosen with various stomach conditions, as well as with no complaints referable to that organ. Among the diagnoses were peptic ulcer, "gastritis," and gastric carcinoma. The reactions of the patients to the administration of eugenol were as follows: Many of them experienced nausea, but this is a frequent occurrence in intubated patients. One patient vomited in response to the eugenol, and another experienced slight pain. A third subject, a 60-year-old woman, experienced severe reactions about 5 minutes after administration of the stimulus. These consisted of pain, profuse sweating, pallor, and semiconsciousness. Approximately half of the eugenol was withdrawn promptly; about 10 minutes later she still experienced weakness and headache but had recovered sufficiently to continue with the procedure. In contrast with such disturbances, several patients stated voluntarily that they felt better after the treatment, perhaps because of the carminative action of the chemical. Some even asked for a repetition of the procedure on a subsequent visit to the hospital. Preliminary determination in dogs of the toxicity of eugenol administered by stomach tube indicated that the dose used in these tests was within safe limits. Detailed toxicity studies will be reported elsewhere.

For cytologic study of the aspirates, smears were prepared and following a period of air-drying were stained with toluidine blue. Two staining techniques were employed. The earlier one (*2*) preserved the columnar cells poorly and was replaced by a more satisfactory procedure. The smears of dog secretion shown in our previous report at this conference were prepared by the later method (*3*). This technique differs in several essentials from that reported by Papanicolaou (*4*), and it is our intention to use both of them in our systematic studies on human beings.

The foregoing method for obtaining mucus secretion in man is an adaptation of standard clinical procedure and is easily performed. It yields considerable volumes of mucoid material; of 111 quarter-hour samples, 60 percent were greater than 10 cc. Mucin is present in considerable quantities, as evidenced by the viscosity and

[1] This investigation is being conducted with the aid of a grant from the National Cancer Institute.
[2] The authors wish to express their thanks to Miss Rosette Spoerri for her assistance in some of these experiments.

tenacity of the material, and by the metachromatic staining of the smears. As with the dog, mild irritation results in a striking increase in desquamation. The desquamated material consists not only of individual columnar cells but also of clumps and ranks of these elements. Squamous-epithelial cells, leukocytes, and bacteria are also frequently noted in the preparations.

It is evident, therefore, that we now have a satisfactory technique for studying various aspects of the physiology of gastric mucus secretion in man. Furthermore, once it has been established that cancerous epithelium also responds to eugenol by the shedding of large numbers of cells, the technique may prove of value in the recognition of gastric adenocarcinoma in the early stages of its development.

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GASTRIC ACIDITY BEFORE AND AFTER THE DEVELOPMENT OF CARCINOMA OF THE STOMACH[1]

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INTRODUCTION

Gastric secretory function is subnormal in patients who have carcinoma of the stomach (*1–3*). For some reason, the percentage (20) of anacidity and the mean concentration of free hydrochloric acid (38 units) found among normal persons of the same sex and age have been, respectively, increased to around 60 percent and reduced to 26 clinical units among cancerous persons (Comfort and Vanzant). When does the reduction take place? Do persons in whom gastric cancer subsequently develops start life with a low mean secretory activity, or do they start life with a normal mean secretory capacity that is partly lost before cancer develops, or does some of the reduction take place after cancer develops? What is responsible for the loss of secretion? In 1937 Butsch, Eusterman, and Comfort (*4*) asked these same questions and presented data bearing on the answers. At this time we shall present similar but more extensive data.

MATERIALS AND METHOD

A modification of the Ewald test meal used to determine gastric acidity has been described previously. The statistical technique of Vanzant, Alvarez, Eusterman, Dunn, and Berkson (*5*) has been followed.

To obtain the records of those patients for whom an analysis of the gastric contents had been made before the development of gastric cancer, we first separated, from the total number of cases in which gastric cancer had been verified by surgical exploration, the records of 1,347 patients who had been examined at the Mayo Clinic before the diagnosis of cancer was made. We then searched the records of these patients to find those for whom gastric analysis had been performed, and we found 277 for whom 1 analysis or more had been carried out 2 or more years before the diagnosis of carcinoma of the stomach was established.

We are presenting the data obtained from the records of these 277 patients. The males numbered 203, females 74. The ratio of males to females is similar to that in other series of gastric cancer. For 186 of the 277 patients, gastric analysis satisfactory for statistical purposes also was performed at the time of the diagnosis of cancer. In the remaining 91 of the 277 cases, gastric analysis either was not done at the time cancer was found or some operative procedure had been carried out after the initial test meal and prior to the development of cancer, rendering the values obtained by gastric analysis inaccurate for statistical purposes.

The distribution of patients according to age at the time of the initial gastric analysis is given in table 1. Patients of all ages from the second to the eighth decades of life were seen. The average age of the patients at the time of the first test meals was 48.5 years.

TABLE 1.—*Gastric acidity; initial gastric analysis in relation to age*[1]

Age (in years)	Total cases	Patients with achlorhydria		Patients with acid	
		Number	Percent	Number	Mean units
10-19	1	0		1	26.0
20-29	15	2	13.3	13	36.3
30-39	60	18	30.0	40	40.4
40-49	80	41	51.3	41	31.2
50-59	77	40	51.9	37	30.6
60 or more	44	26	59.1	18	33.3
Total or average	277	127	45.8	150	35.3

[1] The series included in this study comprises only patients who had at least 1 gastric analysis 2 or more years prior to the time of diagnosis of a malignant lesion.

The distribution of patients according to gastric acidity at both the initial gastric analysis and the time of diagnosis of gastric cancer is given in table 2. The distribution of patients according to the interval of time elapsing between the initial gastric analysis and the diagnosis of cancer is given in table 3. Cases in which the interval of time between the initial gastric analysis and the diagnosis of cancer was less than 2 years have not been included. Attention is called to the fact that the interval was as long as 39 years and averaged 11.2 years. The mean interval was the same among patients whose gastric contents were achlorhydric and among those whose gastric contents contained free acid at the time of the initial test meal.

The diagnoses made at the time of the initial test meal are given in table 4. The mean deviation of free acidity from standard normals for each group computed according to the technique of Vanzant, Berkson, and Alvarez (*6*) also is given.

It is realized that the method of selection of these cases, consisting as it did of taking only those patients for whom gastric analysis had been performed in visits previous to the one in which cancer was diagnosed, renders the series a selected one, and not necessarily representative of gastric cancer as it occurs in the general clinic population.

[1] Read before the Gastric Cancer Conference, Chicago, December 5 and 6, 1946.

TABLE 2.—*Gastric acidity at initial gastric analysis and at time of diagnosis of gastric carcinoma*

Acid (units)	Cases of gastric acidity at—			
	Initial gastric analysis		Time of diagnosis	
	Number	*Percent*	*Number*	*Percent*
1-9	12	8.0	4	6.9
10-19	28	18.6	11	19.0
20-29	25	16.7	18	31.0
30-39	27	18.0	7	12.1
40-49	27	18.0	9	15.5
50-59	15	10.0	4	6.9
60 or more	16	10.7	5	8.6
Total cases of acidity	150	100.0	58	100.0
Mean free acid	35.3		31.6	
Cases of achlorhydria	127	45.8	128	68.8
Total cases	277		186	

TABLE 3.—*Intervals between the gastric analysis and the diagnosis of cancer in relation to gastric acidity at the time of the initial test meal*

Interval (in years)	Cases of acid at initial examination		Total cases	
	Achlorhydria	Free acidity		
	Number	*Number*	*Number*	*Percent*
2	8	7	15	5.4
3	9	22	31	11.2
4	10	13	23	8.3
5-9	38	30	68	24.6
10-14	27	32	59	21.3
15-19	16	24	40	14.4
20-24	12	12	24	8.7
25-39	7	10	17	6.1
Total	127	150	277	100.0
Mean, years	11.1	11.2	11.2	

TABLE 4.—*Clinical diagnosis at time of initial gastric analysis*

Clinical diagnosis	Cases of—				Deviation from normal units [1]
	Achlorhydria		Free acidity		
	Total	Verified surgically	Total	Verified surgically	
	Number	*Number*	*Number*	*Number*	
Pernicious anemia	23	.....	30	14	+3
Duodenal ulcer	.....	.....	30	26	−4
Gastric ulcer	3	3	9	2	−16
Peptic ulcer	.....	.....	4	4	−28
Chronic gastritis	6	2	0	.....	.....
Gastric polyposis	1	1	18	7	−5
Cholecystitis	21	11	.....	.....	.....
Functional gastrointestinal disease	28	.....	46	.....	−13
Other gastrointestinal diseases	29	.....	6	.....	−14
Nongastrointestinal disease	16	.....	7	.....	−2
Total	127	.....	150	.....	.....

[1] Mean deviation of free acidity from normal.

It is interesting, however, to note the proportions of some of the diagnoses as they were made at the time of original examination. For instance, in our series 23 patients of the 277, or 8 percent, had a diagnosis of pernicious anemia, whereas in the general clinic population the incidence of this disease is about 0.2 percent. Similarly, duodenal ulcer had an incidence in this series of 11 percent, whereas in the clinic population the incidence is about 3 percent. Gastric ulcer in this series has an incidence of 12 percent whereas in the clinic population the incidence is about 0.2 percent. Thus it is seen that the incidence of these conditions in our series is very high on a comparative basis. In the clinic population the incidence of duodenal ulcer, benign gastric ulcer, and pernicious anemia in patients in whom gastric cancer subsequently develops has not been determined, but it is suspected that the incidence of these conditions in our series is high.

In all cases, the surgical observations, results of roentgenologic examination, or the interval of 2 years or more between the initial gastric analysis and the diagnosis of cancer make it highly improbable that cancer was present at the time of the initial gastric analysis.

GASTRIC ACIDITY BEFORE THE DEVELOPMENT OF CARCINOMA OF THE STOMACH

Among the 277 patients for whom gastric analysis was done 2 or more years before cancer was diagnosed, 127 (45.8 percent) had achlorhydric gastric contents and 150 (54.2 percent) had gastric contents containing free acid. In the 150 cases in which the gastric contents contained free acid, the mean free acid was 35.3 clinical units. In short, before cancer developed, the incidence of anacidity was greater by 24 percent, and the mean free acidity was smaller by 3 clinical units than would be expected for a group of normal persons of the same sex and age. The mean free acidity in the group of patients (69) who had peptic ulcer and also free acid in the gastric contents was 39.8 units, and that of the remaining patients who had free acid in the gastric contents was 27.8 units. In spite of the number of patients with peptic ulcer, who had high mean free acidity, the mean gastric secretory activity of the precancerous stomach in this group is below the standard normal.

The percentage of patients who had achlorhydria, for each decade of life, in both the present series of 277 and in groups of normal persons of the same sex and age is shown in figure 1. The initial examination was made at an average of 11 years prior to the time of diagnosis. It is obvious that the percentages of achlorhydria in this group of precancerous persons is greater in each decade than in normal persons and that the peak is reached in the fifth decade rather than in the seventh decade, as is the case among normal persons. The defect in the gastric mucosa responsible for achlorhydria appears to occur more frequently in each decade and to reach its peak incidence earlier

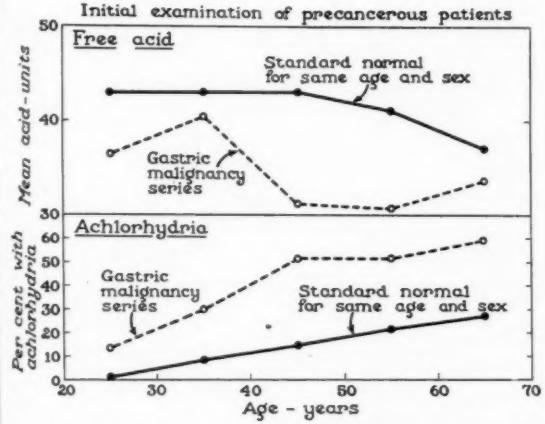

FIGURE 1.—Gastric acidity among persons in an experimental series at the time of initial examination, compared with gastric acidity among normal persons. At each age the percentage of persons with achlorhydria was higher, and for those who had acidity the mean acid was lower, than was true in a group of normal persons of the same age and sex as those in the experimental series.

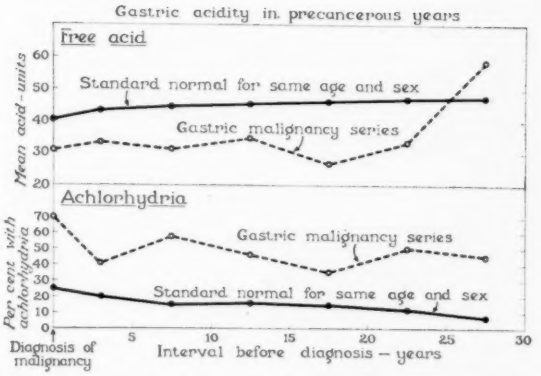

FIGURE 2.—Gastric acidity at progressively longer intervals before the time of diagnosis of gastric cancer. At all intervals recorded, and as long as 25 years prior to the diagnosis, the picture was one of low acidity as compared with normal. The percentage for achlorhydria was higher, and for those who had acidity the mean acid was lower than for a group of normal persons of the same age and sex as those in the experimental series.

in the precancerous person than in the normal person.

The mean acidity for each decade of life, for both normal persons and precancerous persons, is also charted in figure 1. The mean acidity is lower for the precancerous group as early as the third decade, is lower for each decade than it is in the normal group, and is lower in the fifth, sixth, and seventh decades than in the third and fourth decades. Again, it may be said that the defect responsible for lowering of the gastric acidity is present as early as the third decade, that it lowers gastric acidity in each decade below the standard normal, and that it has a greater effect in the later years of life than in the early years.

Gastric acidity considered in relation to the interval in years before the diagnosis of cancer was made is given in table 5, and is plotted against the acidity of groups of normal persons of the same sex and age in figure 2. The data obtained from 531 test meals ingested by the 277 patients in this series, both before and after cancer was diagnosed, are included.

The contrast in data from the two groups is striking. The percentage of achlorhydria among precancerous persons is greater than the standard normal at each interval and is greater than 40 percent at all intervals in years, at 10, 15, 20, and even 25 years before the development of cancer. Similarly, the mean free acidity is lower than normal even as long as 10, 15, 20, and 25 years before the development of cancer. In general, the percentage of achlorhydria seems to increase, and the mean free acidity seems to decrease as the time approaches for cancer to develop, but the rate of decrease of secretory activity, if present, is not greater than that seen in normal persons.

The defect responsible for lowered secretory activity in some precancerous persons seems to appear early in life and to precede the development of cancer by as long as 20 to 25 years.

CHANGES IN SECRETORY ACTIVITY IN THE INTERVAL BETWEEN THE INITIAL GASTRIC ANALYSIS AND THE DIAGNOSIS OF GASTRIC CANCER

Among the 227 patients for whom gastric analysis was done at the time of initial examination, 186 also had gastric analysis done at the time of the diagnosis of cancer. Of the 127 patients who had achlorhydria initially, 94 were examined for gastric acidity at the time the diagnosis of gastric cancer was made. Of the 94, 89 (95 percent) were

TABLE 5.—*Gastric acidity in relation to interval before diagnosis*[1]

Interval before diagnosis (in years)	Total cases	Cases of achlorhydria		Cases with acid	
		Number	Percent	Number	Mean
0	186	128	68.8	58	31.6
1	12	5	41.7	7	24.9
2	23	12	52.1	11	31.3
3	39	11	28.2	28	35.4
4	28	14	50.0	14	34.6
5-9	87	50	57.5	37	31.1
10-14	69	32	46.4	37	34.9
15-19	44	18	40.9	26	26.8
20-24	26	13	50.0	13	33.1
25+	18	8	44.4	10	58.6

[1] 277 patients; 531 gastric analyses.

found still to have achlorhydria. Thus, practically none of the patients who had achlorhydria at the time of the first examination showed acid in the test meal at the time of diagnosis.

Of the 150 patients whose stomachs contained free acid initially, 92 were given test meals at the time the diagnosis of cancer was made; of the 92, achlorhydria had developed in 39 (42.3 percent) (table 6). The mean free acidity of the gastric contents of the remaining 53 was 31.4, lower by only 3.9 units than that of the 150 patients with free acidity at the time of the initial test meal.

The 92 patients with free acidity initially who ingested test meals both at the time of initial analysis and at the time of diagnosis of cancer have been grouped acording to free acidity in table 6. The percentage of patients in whom achlorhydria developed was greatest among those patients with a low mean acidity, and smallest among those with a high mean acidity at the time of the initial gastric analysis. The lower the initial mean free acid, the greater is the tendency for the gastric contents to become achlorhydric.

TABLE 6.—*Patients with acidity initially, subsequent reduction of acidity*

Initial acidity (in units)	Cases	Patients with acidity at time of diagnosis			
		Achlorhydria		Free acidity	
		Number	Percent	Number	Mean
1–19	29	20	68.9	9	20.3
20–39	34	13	38.2	21	27.8
40 or more	29	6	20.7	23	40.0
Total or average	92	39	42.3	53	31.4

GASTRIC ACIDITY AT THE TIME OF THE DIAGNOSIS OF CANCER

Between the time of the initial gastric analysis and the diagnosis of cancer, intervals of 2 to 39 years or more passed (table 3). Cancer had developed within 2 to 4 years, inclusive, in 69 patients, and within 2 to 9 years, inclusive, in 137 patients. Cancer had developed within 10 to 19 years, inclusive, in an additional 109, and within 20 to 24 years after the initial gastric analysis in an additional 24 patients. In the remaining 17 cases, 25 to 39 years elapsed before cancer developed. The interval averaged 11.2 years, and the mean age of the patients increased from 48.5 to 59.7 years.

At the time of the diagnosis of cancer, the percentage of patients who had achlorhydria had increased from the initial 45.8 to 68.8 percent, or from +23 to +53 percent above the standard normal. Similarly, the mean for acidity had decreased from an initial 35.3 to 31.6 units, or from −3 to −5 units below the standard normal.

Vanzant and Comfort found that the percentage of achlorhydria and the mean free acidity in a group of 619 men with gastric cancer were, respectively, 62.8 percent and 28.2 units, and in a group of 186 women with gastric cancer, respectively, 55.9 percent and 24.6 units. Comparison of these values with those obtained in this series of 186 cases shows that the percentage of achlorhydria and the mean free acidity are higher in the present series, but that the differences are not great. The large number of cases of pernicious anemia in the series may be partly responsible for the higher percentage of achlorhydria, and the large number of cases of duodenal and gastric ulcer may be partly responsible for the higher mean free acid in this series than was true in the aforementioned series.

COMMENT

These data show that the mean gastric secretory activity of 277 persons in this series in whom gastric cancer later developed was already subnormal at the time of the initial test meal which was ingested and analyzed at a mean interval of 11.2 years before cancer was diagnosed. The mean gastric secretory activity was subnormal as early as the third decade of life; it was subnormal to a greater degree in the fourth and fifth decades than in the third decade; and thereafter it leveled off at a point lower than that seen in the third and fourth decades. The mean gastric secretory activity was subnormal at the time of ingestion and analysis of the first test meal as long as 25 or more years before the diagnosis of cancer, and it remained so. In the interval between the first test meal and the diagnosis of cancer a further lowering of secretory activity occurred.

Two pertinent questions may be asked: (1) What is responsible for the depression of gastric acidity below normal at the time of the initial test meal, long before cancer has developed? (2) What causes the further reduction of secretory activity between the time of the first test meal and the diagnosis of cancer?

Three hypotheses may be advanced in explanation of the depression of gastric acidity at the time of the first test meal as well as at the time of the diagnosis of cancer.

First, a hypothesis based on developmental aspects assumes that the subnormal secretory activity of this group of persons was subnormal at birth and is the result of a defect in the secretory mechanism. This hypothesis is based on the occasional demonstration, in the first years of life, of achlorhydria and hypoacidity (*5, 7–9*). Such evidence of a developmental defect is not convincing because immaturity of the gastric mucous membrane, which Guiss and Stewart (*10*) found to be present up to the second decade of life, may be responsible for the low values observed in these years.

The demonstration that the gastric secretion of certain infants and children remains achlorhydric and hypochlorhydric from birth would be helpful in establishing the frequency with which a developmental defect is responsible for lowered gastric acidity.

The second hypothesis assumes that the gastric mucosa is abnormally vulnerable to trauma of various types, that a degenerative process appears prematurely, that the acid and perhaps the mucoid cells atrophy, and that hypoacidity and achlorhydria appear with the passage of years. This hypothesis has not been disproved and cannot be discarded.

The third hypothesis attributes the lower secretory activity to the destruction of acid-secreting cells by chronic atrophic gastritis. Available evidence favors this hypothesis:

(1) Chronic atrophic gastritis is the only diffuse disease of the gastric mucosa capable of destroying the acid-secreting cells in large numbers, and it is present in a high percentage of cases of gastric cancer [2] (*10–15*), and in all cases of pernicious anemia (*16*). As the term is used today, "chronic atrophic gastritis" means lymphoid collections in the mucosa; irregularity, thickening, and fibrosis of the muscularis mucosae; transformation of the gastric mucosa into a mucosa of the intestinal type (intestinal metaplasia); loss of the characteristic gastric glands with their chief and parietal cells in the fundic portion of the stomach, and replacement by a mucosal pattern characteristic of the pylorus and antrum (pylorization of the fundic mucosa) (Stout *14*); and mucosal cysts. These changes also are referred to as "chronic gastritis" and "residual lesions of ulcerative gastritis" (*17*). The particular portions of the pathologic process important to the discussion of gastric acidity are atrophy, or loss of the chief cells, which reduces the secretion of acid.

(2) The frequency of occurrence and the severity of the gastritis seem to be roughly proportionate to mean secretory activity. Thus, atrophic gastritis is more frequently present in the carcinomatous stomach (*10-12*) and in the stomachs of patients with pernicious anemia (*16*) where the mean secretory activity is much below normal, than it is in the "normal" stomach (*10–12*), or in the stomach of the patient who has ulcer (*12–14*) where the mean secretory activity is at or above normal (*18*). A marked degree of atrophy of the chief cells and replacement with mucoid cells occurs more frequently in gastric cancer and in pernicious anemia, where the mean secretory activity is much below normal, than in normal persons (*12*), and in gastric or duodenal ulcer (*14*), where the mean gastric secretion is more normal or above.

(3) The pathologic studies of Orator and Baker show that chronic gastritis of a marked degree involving the acid-secreting portion of the carcinomatous stomach is usually present when achlorhydria is present and that it is usually absent when free hydrochloric acid is secreted. More specifically, Orator and Baker showed that the acid-secreting cells are absent or greatly reduced in number when achlorhydria exists and are present when acid is secreted. Proof of a definite correlation between degree of atrophy and mean gastric acidity awaits more quantitative data than those now available.

(4) Increase in the frequency of occurrence of atrophic gastritis with increasing age recalls that gastric secretory activity decreases as age increases (*9, 10, 14*) both in normal persons (*5, 19*) and in patients who have carcinoma of the stomach (*1, 2*). The possible relationship between atrophic gastritis and subnormal gastric acidity in precancerous and cancerous stomachs cannot be ignored.

The further decrease in mean secretory activity in the interval between ingestion and analysis of the first test meal and the diagnosis of cancer may be attributed (1) to progression of a degenerative process, if present, or of the chronic inflammatory process present at the time of the first test meal, and (2) to the cancer itself. It is possible that the cancer decreases secretory activity (1) by producing gastritis, (2) by destruction of acid-secreting cells when the cancer is located in the fundus and body of the stomach, (3) by increasing the amount of neutralizing fluid in the stomach by the exudation of serum from the surface of the tumor, and (4) by producing vitamin-deficiency states capable of reducing gastric acidity (*20–22*). Vanzant and Comfort in a study of gastric acidity in cancer pointed out that the mean secretory activity is lower when the mean size of the cancer is large than when the mean size of the cancer is small. This suggested that the growth of the tumor depresses gastric acidity. However, Butsch, Eusterman, and Comfort, finding in a small series of cases that the mean size of cancer developing in the presence of achlorhydria is greater than that of cancer developing in stomachs secreting acid, suggested another interpretation of this relationship between size of cancer and gastric acidity, namely, that the cancer becomes larger before symptoms force the patient to seek examination when achlorhydria is known to be present before the development and diagnosis of cancer than when free acid is known to have been present. Actually, gastric acidity has been observed to fall in the cancerous stomach [3] (*23–25*), but the data from this series of

[2] BAKER, C. P.: Quoted by Comfort, Butsch, and Eusterman (*4*).

[3] KOCH, R. D.: Cited by Robertson (*24*).

cases are convincing that most of the depression preceded and did not follow the development of cancer.

Finally, the excessive production of an inhibitory substance or agent by cancerous tissue or by the gastric mucosa of cancerous stomachs, such as described by Brunschwig and associates (*26–31*), might conceivably play a role in the production of subnormal acidity both before and after the development of cancer.

SUMMARY AND CONCLUSIONS

In a series of 277 cases of gastric cancer in which gastric analysis was performed once or more 2 or more years before gastric cancer was diagnosed, the mean secretory activity had been subnormal at a mean interval of 11.2 years before the diagnosis of cancer was made.

A subnormal, mean gastric secretory activity was characteristic of these precancerous patients regardless of the decade of life in which the initial test meal was ingested and analyzed. This was true as early as the third decade but was more marked in the later decades.

A subnormal, mean gastric secretory activity was characteristic of these patients during all intervals in years before cancer was diagnosed and as long as 20 to 25 years and longer before cancer developed.

The mean secretory activity of the 186 patients for whom gastric analysis was carried out at the time of the diagnosis of cancer, as well as at the initial investigation, decreased in the interval between the 2 analyses. The lowering of mean secretory activity tended to occur more frequently in those cases in which the mean free acidity initially had been lower than in those in which initially it had been higher.

In these patients the process or processes responsible for the low mean gastric secretory activity had been active early in life, and in a considerable number of patients many years before the development of cancer. The process had depressed mean gastric acidity in a greater percentage of patients in the later than in the early decades of life. It appears that the process responsible for the lowering of gastric acidity was a progressive one. This process seems to have been selective, because gastric acidity did not appreciably decrease in all cases.

Evidence now available tends to support the hypothesis that atrophy of the gastric mucous membrane is a process responsible for an important part of the depression of mean gastric secretory activity before the development of gastric cancer.

Gastric cancers in this series of cases developed in stomachs of lower-than-normal mean secretory activity, many of them in the unhealthy stomach, diseased with chronic gastritis and peptic ulcer.

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THE ROLE OF CANCER-PREVENTION CLINICS IN THE DETECTION OF EARLY GASTRIC CANCER

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Before one can evaluate adequately the role of cancer prevention clinics in the detection of early gastric cancer, the development and rationale of this special type of clinic should be reviewed. In general, cancer-prevention clinics have been concerned with the examination of readily accessible organs, such as the breast and cervix in which malignancies are prone to occur. The second feature common to these clinics has been the periodic examination of individuals who are apparently in good health.

Some have maintained that the word "prevention" is inappropriate, since no cancers are indisputably prevented but simply discovered. This seems a narrow viewpoint, for it can be fairly stated that some lesions are indeed precursors of cancer and by their early eradication malignancy can be prevented.

Since 1937 L'Esperance (*1*) in New York and Macfarlane (*2*) in Philadelphia have made periodic examinations of sizable numbers of women in an attempt to discover early cancers of the breast and uterus. Their reported statistics indicate that this method does reveal unsuspected malignancies; but of equal importance, as Macfarlane has emphasized, is the fact that nearly one-third of presumably healthy women over the age of 30 at some time were found to display benign cervical lesions which might predispose to cancer. The eradication of these cervical lacerations, erosions or polyps probably will prevent the ultimate development of many malignancies.

Another point which this type of examination has underscored is that advanced malignancies may be present with symptoms of exceedingly brief duration. Therefore, throughout the Nation there now have appeared, to a high degree as a result of the vigorous encouragement of the Donner Foundation (*3*), many cancer-prevention clinics designed to examine periodically persons who are seemingly healthy. There is no doubt that such an approach will be profitable both in regard to the neoplasms discovered but also in the education of the public concerning cancer. It is quite obvious, however, that these methods for the detection of early cancers, although successful, are applicable only to those sites of malignancy which are readily visualized. In addition to cancers of the breast and cervix, malignancies of the skin, thyroid, and lymph nodes, for example, may be discovered. Internal cancers present quite another problem, for, unless relatively far advanced, the physical signs of their presence may be absent or very meager. The victim feels no lump and experiences no symptoms to which he attaches significance; and when gastric malignancy is suspected, the ultimate use of the barium meal or of the gastroscope is necessary to detect small neoplasms.

With this background, the stage was set to attempt the early diagnosis of gastric cancer by analogous methods. In a cancer-prevention clinic, in actual practice, a scrupulously careful history, together with data about the familial incidence of cancer, should be obtained from all, and a detailed physical examination should be made including, in women, a thorough pelvic examination. Blood counts, serologic tests, urinalyses, and roentgenologic examination of the chest should be made routinely. We feel that cancer-prevention clinics, although established as independent units, should have the benefit of all consultative services of the general out-patient diagnostic clinics. All persons over the age of 40 who give a history of significant dyspepsia, or fatigability and weight loss, or in whom an otherwise unexplained anemia is found, should receive in addition a roentgenologic examination of the gastrointestinal tract. In the evaluation of the importance of indigestion, it may be helpful to bear in mind the facts emphasized by Allen (*4*), namely, in patients over the age of 50 with symptoms of less than a year's duration, any lesions found in the stomach proved to be cancer five times as often as benign ulcer; while if symptoms had been present for over 5 years, the reverse was true in the same age group. Since the absolute clinical differentiation between various types of organic gastric disease and so-called functional indigestion is quite impossible, a barium meal examination of those over 40 is necessary.

All patients in the cancer-prevention clinic with suspected organic disease of the stomach should undergo repeated examinations until it has been determined that the stomach is not the site of a malignancy. This requires an alert group of workers, including a radiologist and gastroscopist. Zealous follow-up studies of all cases of gastric ulcers and the advice that they be surgically removed if full healing does not occur promptly will insure the earlier diagnosis of some malignancies. The question here is not whether a benign ulcer will transform into a cancer, but rather that at a given moment the clinical distinction between a benign and an already malignant ulcer may be impossible. Gastroscopy may aid in the accurate analysis of radiographic abnormalities difficult to evaluate, such as enlarged rugae or antral deformities. Here, again, is exemplified the need for close team work so that resectable gastric malig-

nancies may be promptly discovered, yet on the other hand unwarranted laparotomies may be avoided.

However, one large loophole remains: In spite of examination by barium meal of all patients with symptoms, we shall fail to discover the silent gastric malignancies. Evidence from our clinic vividly demonstrates this point.

Between January 1, 1930, and January 1, 1946, 333 persons with surgically proved cases of gastric carcinoma were operated upon at the University of California Hospital. Among them were 24 (7.2 percent) who had had symptoms of dyspepsia, weight loss, abdominal pain, or weakness for 2 months or less. The size and extent of these tumors were appalling. In one-third of these 24 cases, at least one-quarter of the stomach was involved by the growth, and in all but 2 of the 24, the carcinoma had extended or metastasized beyond the confines of the stomach (table 1). Thus the inference is obvious, since these tumors could hardly attain such size in 2 months, that a silent phase of development of unknown length had been present.

For this reason it has seemed desirable to ascertain the frequency of gastric cancer in symptomless individuals as a necessary adjunct to the work of a prevention clinic proper. St. John and his associates (*5*) have made such a conscientious attempt to discover unsuspected gastric neoplasms by routine barium-meal examinations of normal individuals. Three unsuspected gastric malignancies were found among the 2,413 persons thus examined. We have made a similar survey (*6*) and discovered no gastric malignancies among 500 normal men over the age of 45, in whom no symptoms referable to the gastrointestinal tract were present. The rationale of these undertakings was precisely that of a chest survey, whereby we attempt to discover early tuberculosis prior to the display of symptoms. It appears that such surveys to discover silent gastric cancer are not worth while because of the meager number of malignancies discovered.

A more profitable approach is to examine periodically all cases of pernicious anemia, as Rigler (*7*) has advocated. Patients with histamine-proved anacidity should probably be examined likewise since a significant proportion of them have atrophy of the gastric mucosa (*8*) which appears in certain instances to be the soil on which gastric neoplasms develop. Whether certain forms of bona fide gastritis warrant special scrutiny regarding their being a precursor of cancer cannot be fully decided upon from the present evidence (*9*).

TABLE 1.—*Surgically proved gastric carcinomas with symptoms of 2 months' duration or less*

Case No.	Sex	Age	Duration of symptoms	Type of symptoms	Gastric lesion found	Metastasis (M) [1] or extension (E) [2] of tumor
		Years	*Months*			
1	F	69	0	None. Epigastric mass discovered on physical examination.	Polypoid antral tumor, 5 cm. in diameter	Pancreas (E).
2	F	53	1	Epigastric postprandial pain	All of fundus and cardia	Omentum (E), nodes (M).
3	F	59	1	Epigastric pressure with moderate pain	Ulceration of body, 5 x 3 cm., with infiltration	
4	M	33	1	Epigastric pain, hematemesis, loss of 10 pounds.	Malignant ulcer, 4 cm. in diameter, in lower body.	Nodes (M).
5	M	65	1	Anorexia, nausea, vomiting	Infiltration in antrum, 3 x 2.5 cm	
6	M	67	1	Nausea, vomiting, loss of 20 pounds	All of lesser curvature except proximal 5 cm.	Gall bladder (M), nodes (M).
7	M	57	1½	Nausea, vomiting	All of distal third of stomach	Nodes (M), omentum (E).
8	M	61	1½	Epigastric cramping, postprandial vomiting, loss of 10 pounds.	Polypoid antral tumor, 7 x 7 cm	Nodes (M).
9	F	74	1½	Epigastric pain, vomiting	Polypoid antral tumor, 5 x 7 cm	Nodes (M).
10	M	64	1½	Abdominal pressure, vomiting	Ulcer enclosing pylorus	Nodes (M).
11	M	52	2	Epigastric fullness, dysphagia, loss of 15 pounds.	Polypoid cardiac mass, 5 cm. in diameter, extending into esophagus.	Nodes (M).
12	M	55	2	Dysphagia, loss of 25 pounds	Infiltration, 10 cm., at cardia on lesser curvature.	Nodes (M).
13	M	61	2	Anorexia, vomiting, loss of 20 pounds	Wide annular constriction, 5 cm., of lower body with ulcer, 1.5 cm. in diameter.	Omentum (E), nodes (M), pancreas (M).
14	M	63	2	Epigastric pressure with steady pain	Fungating carcinoma, 4 x 4 cm., in antrum	Nodes (M).
15	M	80	2	Epigastric heaviness, mild nausea	Antral infiltration, 10 x 7 cm	Omentum (E).
16	F	72	2	Mild epigastric pain, loss of 8 pounds	Polypoid antral tumor, 5 x 5 cm., with infiltration halfway up lesser curvature.	Liver (M).
17	M	65	2	Epigastric pain, vomiting	Nearly all of pyloric antrum	Nodes (M).
18	M	46	2	Dull epigastric pain, vomiting, loss of 25 pounds.	Polypoid antral tumor, 5 cm. in diameter	Pancreas (E).
19	M	54	2	Epigastric postprandial pressure, nausea, vomiting.	Irregular antral mass, 6 cm. in diameter	Omentum (E).
20	M	48	2	Upper abdominal dull pain, vomiting, loss of 10 pounds.	All of greater curvature, antrum to diaphragm	Nodes (M).
21	M	76	2	Epigastric postprandial pressure, nausea, loss of 15 pounds.	Antral tumor, 8 cm. in diameter	Liver (M), nodes (M), cul-de-sac (M).
22	M	56	2	Epigastric postprandial pain, anorexia, loss of 30 pounds.	Nearly entire stomach	Nodes (M), omentum (E), pancreas (E).
23	M	66	2	Dull pain in left lower quadrant, anorexia, loss of 30 pounds.	Two-thirds of mid-stomach	Nodes (M), omentum (E).
24	M	63	2	Dull epigastric pain, anorexia, loss of 10 pounds.	Entire body of stomach, fixed	Liver (M), nodes (M), omentum (E).

[1] M, Metastasis, discrete focus, independent of primary tumor.
[2] E, Extension of primary tumor to contiguous organs.

The cancer-prevention clinic should be able to utilize promptly any recent advances which might be helpful in gleaning from the general population those harboring early carcinomas or their precursors. Further research in such directions is needed, and thus the cancer-prevention clinic must maintain continuous liaison with both laboratory and clinical investigators. Fruits of such work which should immediately be utilized are exemplified by the studies of Rigler and of Papanicolaou (*10*).

In the years ahead, the statistical studies which may be made of patients seen in such clinics will be most valuable. Cancer may be made a reportable disease, and thereby the incidence of various types will be made known, but only from such unique studies as may some day be derived from prevention clinics can we hope to learn certain features of cancer's natural development in human subjects.

A final role of any cancer-prevention clinic is educational. Physicians who are associated with such clinics or medical students who may participate soon develop an awareness of the subtlety of the symptoms of early cancer and the need for a prompt and thorough evaluation of all symptoms suggestive of its presence. Education of the laity regarding some of the more obvious signs of cancer is already under way. As far as gastric cancer is concerned, the grave danger of self-medication with various remedies for dyspepsia must be continuously stressed. Pharmacists in the past have displayed efficiency and eagerness in aiding campaigns against the self-treatment of venereal diseases. They have, with Dr. Bower, of Philadelphia, some years ago, brought about a significant reduction in the incidence of complicated appendicitis by warning customers, both by word and printed label, of the hazard of taking cathartics in the presence of abdominal pain. A similar approach to the problem of the detection of gastric cancer seems in order, and perhaps by our enlisting the aid of the members of the pharmacy profession, sufferers from so-called indigestion will realize that a prompt and adequate medical investigation of their symptoms is needed. It is no doubt still sadly true, as Pack and Gallo (*11*) pointed out 8 years ago, that fully half the patients with cancer of the stomach temporize more than 3 months after the onset of symptoms before seeking medical advice.

SUMMARY

In cancer-prevention clinics, the periodic examination of those in apparent health has proved a profitable method of discovering unsuspected accessible cancers. The early diagnosis of gastric cancer in such clinics depends upon the prompt use of the roentgenologic examination of the gastrointestinal tract of all persons with dyspepsia and all with diseases, such as pernicious anemia, known to predispose to gastric cancer. Further research must be pursued to discover other types of diseases which may likewise predispose to gastric malignancy. The prime problem before all investigators is to develop means whereby those harboring asymptomatic gastric cancer may be identified. Cancer-prevention clinics should take an active part in the education of the laity and medical profession regarding the part each may play in the early diagnosis of these disorders.

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AN ATTEMPT TO IDENTIFY LIKELY PRECURSORS OF GASTRIC CANCER [1]

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Cardiovascular disease and cancer are the two greatest causes of death in this country, and of the malignancies, carcinoma of the stomach occurs most frequently. Of the 150,000 annual deaths from cancer in the United States, approximately 40,000 are caused by gastric carcinoma. It is estimated that by 1980, 40 percent of the population of the United States will be over 45, so that the incidence of cancer of the stomach will undoubtedly continue to rise as the number of people in the older age group increases further (*1*).

Although the over-all picture of the results of surgery in the treatment of gastric cancer as described by Livingston and Pack (*2*) is not a happy one (2 percent 5-year "cures"), still if a gastric resection is done when the carcinoma is confined entirely to the stomach, the 5-year cures reach 60 percent (*3*). Gastric resection for malignancy can now be done with a mortality rate of approximately 5 percent (*4*), so that it is evident that great strides have been made in the surgical treatment of this disease. Relatively little further improvement can be expected in the end results, unless the diagnosis of gastric carcinoma is made at an earlier period than it has been in the past.

Ketsh (*5*) divides the symptoms of gastric cancer into three periods: (1) The period of absolute latency; (2) the period of relative latency; and (3) the period of apparent disease. It should be the aim of all interested in the clinical problem of gastric carcinoma to diagnose the condition of absolute latency, and preferably individuals who might develop gastric cancer should be sought out, studied, and observed.

In the spring of 1945 a cooperative clinical study group was set up in the University Hospitals embracing the Departments of Pathology, Radiology, and Surgery, in an attempt to define some of the likely precursors of gastric cancer. It was thought that persons with (1) achlorhydria, (2) gastric polyp, (3) pernicious anemia, and (4) also relatives of patients with proved gastric cancer would be more liable to develop carcinoma of the stomach than those who do not fall into these categories. Accordingly on July 1, 1945, this study was started.

METHODS

At the onset of this study, it was planned to subject all male patients 55 years of age or older and female patients 65 or older, registering for the first time at the out-patient clinic of the University Hospitals, to a gastric analysis, employing three successive doses of 0.5 mg. of histamine as a stimulant to gastric secretion. Topfer's reagent was used to test for free hydrochloric acid, and quantitative estimations were made using 0.1N sodium hydroxide and Topfer's reagent and phenolphthalein as indicators. Those patients showing achlorhydria then had their stomachs examined gastroscopically and roentgenographically. The latter examination customarily consisted of fluoroscopic examination after the ingestion of barium, and an appropriate number of routine and spot films were taken for permanent records or to facilitate the diagnosis of obscure lesions. In a number of instances, the patients, for one reason or another, were not given the three conventional doses of histamine. Accordingly these patients have been dealt with as a separate group, the number of histamine injections given being indicated in the patients found to be achlorhydric. If no gastric lesion was found, each achlorhydric patient was given a reappointment slip for a repeat examination in 6 months.

In a previous study, Wetherby (*6*), of this institution, reported on a group of patients, who were observed to be achlorhydric after a single injection of 0.5 mg. of histamine for the year 1940. It was possible to recall 84 of these patients for repeat gastric analysis and roentgenograms of the stomach.

The new patients available for the purpose of this study fell off somewhat behind the predicted number, so that after January 1, 1946, the age level for inclusion in the study was lowered for both male and female patients to 50 years or over.

During the evaluation of the program, it became apparent from the data of Hebbel and Gaviser (table 1), that it would be profitable to study patients with histamine hypochlorhydria as well. Therefore, at present, a roentgen examination of the stomach is planned for all out-patient-clinic registrants 50 years of age or older, with either a

Table 1.—Gastric acidity in carcinoma of the stomach as *related to types of lesions* [1]

Type [2]	Cases	Acid determination	Known histamine	Achlorhydric	Free acid	Acid <20°	Acid >20°
Polypoid (1)	12	8	7	7	0	0	0
Adenocarcinoma (2)	86	63	48	29	19	6	13
(3)	120	116	73	49	24	11	13
Scirrhous (4)	75	57	47	25	22	12	10
Total	293	244	175	110	65	29	36

[1] Data from Hebbel and Gaviser.
[2] Borrmann classification.

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histamine achlorhydria or a hypochlorhydria (less than 20 degrees of free acid). The fact that patients have been reluctant to have repeat gastroscopic examinations has resulted in limiting the use of the procedure to cases where there is a significant doubt about the presence or absence of a lesion after a roentgenogram of the stomach.

From the hospital records, it was possible to contact and re-examine a number of known and suspected patients with pernicious anemia. These patients have had roentgenograms of their stomachs during the period of this study, for they constituted in part the series under the surveillance of Drs. Rigler, Kaplan, and Fink (*7*). All new patients found to have pernicious anemia are also to receive roentgenograms of their stomachs and are to be submitted to gastroscopic examinations whenever feasible.

Detailed information on the family histories of patients with gastric carcinoma has been obtained, a form sheet specifically designed for this purpose being used. As controls, similar factual data have been obtained on patients with noncancerous, gallbladder disease, carcinoma of the rectum and/or colon, hernia, and hemorrhoids. The families of 220 patients with gastric carcinoma have been contacted either by letter or interview. All members over the age of 40 were requested to come into the precursor-gastric-cancer clinic for gastric analysis and roentgenograms of the stomach.

Starting July 1, 1946, it was planned to widen the scope of the project, so as to include more individuals potentially harboring gastric cancer, by adding to the precursor group all out-patient registrants with occult blood in the stool (guaiac) and/or a hemoglobin value on admission of 11.0 gm. or less (Sahli). This study was temporarily suspended about October 1, 1946, but will be resumed when X-ray films are more plentiful.

OBSERVATIONS

From July 1, 1945, to November 1, 1946, 2,225 out-patient-clinic registrants fell in the age group to be studied. The pertinent data are given in table 2. As shown in the table, 310 X-ray examinations of the stomach were made in a group of 350 patients with histamine achlorhydria. To date, in this series 2 persons with unsuspected carcinoma of the stomach have been found. Both were subjected to laparotomy, and the diagnosis of gastric cancer was confirmed. Unfortunately, in both the lesion was far advanced. Three additional patients with carcinoma of the stomach were missed in the course of this study by purely fortuitous circumstances, but it is our belief that by closer scrutiny of patients eligible for inclusion similar errors will be less frequent hereafter. Finally, 1 additional patient was examined by roentgenography, and a small carcinoma of the stomach was overlooked, although re-examination of these films strongly suggested the presence of such a lesion. This carcinoma was recognized at the time of an operation performed upon this patient for another, unrelated condition.

In addition to the foregoing, in the 310 achlorhydric patients having roentgenograms of the stomach, 10 instances of polyp of the stomach were found. No carcinomas or polyps of the stomach have been found in the 18 hypochlorhydric individuals who had X-ray examinations of the stomach. All 84 patients obtained from Dr. Wetherby's list (*6*) had gastric X-ray examinations. No gastric carcinomas were found in this group, but 5 gastric polyps were. Seventy-nine patients with pernicious anemia had roentgenograms of the stomach, but no unusual lesions were found.

Two hundred nineteen patients had their stools examined for occult blood; 40 patients had positive stools, and of these 34 had X-ray examinations of their stomachs. No unsuspected polyps or carcinomas of the stomach were found.[2]

Twenty-one patients (19 over 50 years and 2 under 50) were included in this study because they had hemoglobin levels of less than 11.0 gm. Ten of these patients had roentgenograms of the stom-

TABLE 2.—*Incidence of achlorhydria and hypochlorhydria in patients of age groups eligible for precursor gastric-cancer study*

Number of out-patient registrations	Gastric analyses made			Patients achlorhydric to histamine,[1] according to dose group												Patients hypochlorhydric[2] to histamine			
				3 consecutive doses				2 consecutive doses				Single dose							
	Male	Female	Total	Male	Female	Total	Radiographic examinations made	Male	Female	Total	Radiographic examinations made	Male	Female	Total	Radiographic examinations made	Male	Female	Total	Radiographic examinations made
	Number	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*
2,225	770	483	1,253	164	74	238	245	31	36	67	46	19	26	45	19	20	9	29	18

[1] 0.5 mg. of histamine per dose.
[2] Less than 20 degrees of free hydrochloric acid after 3 consecutive 0.5-mg. doses of histamine.

ach, but no unsuspected gastric carcinomas or polyps were encountered.[3]

Of the families of 220 patients with gastric carcinoma who were contacted, only 40 individuals of 20 families appeared for gastric analysis and roentgenograms. In this group, there were 9 patients achlorhydric to triple histamine, and 12 patients achlorhydric to a single injection of histamine. No gastric cancers or polyps were found.

DISCUSSION

Achlorhydria

The well-recognized frequent association of achlorhydria with cancer of the stomach suggested the acceptance of such a criterion as achlorhydria in this precursor study. From the data of Hebbel and Gaviser (table 1), it is apparent that two-thirds of the patients with gastric carcinoma are histamine-achlorhydric; and if those patients with less than 20 degrees of free acid are included, nearly 90 percent of the carcinomas fall into these 2 groups. Too, a preliminary survey in this clinic of the relationship between histamine achlorhydria or hypochlorhydria, and other malignancies (breast and colon) shows that the incidence of achlorhydria and hypochlorhydria with these malignancies is much less than with gastric cancer.

The need for developing some workable plan for filtering off those cases most likely to harbor a gastric malignancy was additionally substantiated by the studies of St. John, Swenson, and Harvey (*8*) in New York in 1944 and of Dailey and Miller (*9*) in San Francisco in 1945. The former group subjected 2,413 presumably healthy persons over the age of 50 and without gastric complaints to a brief fluoroscopic examination of the stomach after the ingestion of barium. Two silent gastric cancers and one lymphosarcoma were found, an incidence of unsuspected gastric malignancy of 1.24 per thousand patients. No gastric polyps were found. Dailey and Miller reported a series of 500 patients subjected to barium examinations of the stomach. These examinations were performed on presumably normal men over the age of 45 and free from digestive complaints. Three gastric lesions were found, a benign gastric ulcer, a polyp, and antral gastritis in a third patient. It can thus be seen that employing achlorhydria as a screen in this precursor-gastric-cancer study has permitted the discovery of greater numbers of unsuspected gastric malignancies for a given number of X-ray examinations than in the present studies; for of the 412 roentgenograms of the stomach in achlorhydric and hypochlorhydric patients in the Minneapolis study (1945–46) reported herein, 2 unsuspected carcinomas of the stomach and 15 polyps were found. In addition, 1 other carcinoma was not recognized because the X-ray examination of the stomach was interpreted as negative, and 3 other cases were missed through organizational errors.

Gastric Polyps

Fifteen polyps have been uncovered in this study, probably the most fruitful observation to date. Although many authors (Borrmann (*10*), Schindler (*11*), Rigler (*12*)) have indicted polyps of the stomach as precancerous lesions, their actual fate is difficult to evaluate in any given instance as Spriggs and Marxer (*13*) have indicated. It is one of the purposes of this study to attempt to secure a more satisfactory answer to the question whether or not gastric polyps become malignant. To this end, in addition to the 15 polyps discovered in this study, 58 gastric polyps culled from our hospital records from January 1, 1938, to November 1, 1946, are to be placed under careful scrutiny by means of repeat roentgen and gastroscopic examinations. To date, 12 patients with polyps have been operated upon; in 3 instances, local excision was performed; in the remaining 9 partial gastric resection was done. It may be significant that 1 patient, after a subtotal gastric resection for a benign polyp of the stomach, returned 4 years later with an inoperable carcinoma arising from the residual pouch.

Pernicious Anemia

The relationship between pernicious anemia and gastric carcinoma has been noted by a number of observers (Rhoads (*14*) and Kaplan and Rigler (*15*)). Kaplan and Rigler believe that they have shown that the incidence of carcinoma of the stomach in living patients with pernicious anemia is approximately 20 times that of the general population, and that the incidence of gastric cancer in patients dying of pernicious anemia is 12.3 percent, or 3 times the expected autopsy incidence of gastric cancer in patients of the same age group. Atrophic gastritis involving all layers of the stomach is uniformly seen in patients with pernicious anemia (Magnus and Ungley (*16*) 1938)); that atrophic gastritis is a precursor of gastric cancer was strongly contended by Konjetzny (*17*) (1938) and by Schindler (*11*) (1941).

The fact that no gastric carcinoma or polyps were found in the 79 patients with pernicious anemia examined in this study would seem to be at variance with the previous report of Rigler, Kaplan, and Fink (*7*) and suggests that an explanation is in order. The most likely reason for this difference would appear to be that Rigler, Kaplan, and Fink's series represented a group previously unstudied, whereas this series is constituted largely by holdovers from that same series of

[3] Two patients with gastric carcinoma were found in each of these groups, but in each instance the diagnosis was made provisionally from the symptoms presented by the patient.

Rigler, Kaplan, and Fink, these patients exhibiting no polyps or carcinomas at the time of their report and none now. There were 15 new patients with pernicious anemia in this series. Whether time will remove this apparent striking difference in incidence of carcinomas and polyps of the stomach in patients with pernicious anemia remains to be seen. On the basis of previous reports such as those of Rhoads (*14*), Kaplan and Rigler (*15*), and Rigler, Kaplan, and Fink (*7*), one would be justified in believing that some polyps and carcinomas will eventually be demonstrated in our patients with pernicious anemia now under observation.

Relatives of Patients With Gastric Carcinoma

The data obtained on family histories of patients with carcinoma of the stomach (table 3) show that the incidence of carcinoma of the stomach in families of patients with gastric carcinoma was approximately 15.6 percent; in families of patients with noncancerous gall-bladder disease, 10 percent; in families of patients with carcinoma of the colon and rectum, 9.4 percent; and in families of patients with hemorrhoids, 12 percent. The incidence of carcinoma of portions of the body other than the stomach was also obtained for families of patients with gastric cancer and was found to be between 16 and 21.3 percent for each of the groups.

It was felt after compiling these data that there might be some question about the validity of using as controls patients with hemorrhoids and carcinoma of the colon and rectum, so the new control group studied included the families of patients over the age of 45 with noncancerous, gall-bladder disease and the families of patients coming in for the repair of a hernia. It was also deemed important to ascertain the total number of relatives over 45, of each of the groups studied. These results are likewise given in table 3. Although the number of families and relatives is not great, the incidence of carcinoma of the stomach in relatives over 45, of patients with gastric carcinoma, was 1.9 percent; in relatives of patients with gall-bladder disease, 0.89 percent; and in relatives of patients with hernia, 0.79 percent.

A statistical analysis of these results reveals that, although carcinoma of the stomach occurs more frequently in the families of patients with carcinoma of the stomach than in the controls, still the difference is less than twice the standard deviation of the difference and hence is not statistically significant. However, if these small differences continue to appear consistently in the series to be studied, they may be of significance; but it must be borne in mind that patients with cancer

Table 3.—*Incidence of cancer in families or in relatives of patients with gastric cancer and other diseases*

Disease of patient	Number of families	Incomplete information	Families with carcinoma of the stomach			Families with carcinoma elsewhere		
			Number	Percent	Individuals	Number	Percent	Individuals
Carcinoma of stomach	200	13	29	15.6	36	30	16	43
Gall-bladder disease (noncancerous)	200	12	20	10	22	31	16	39
Carcinoma of colon and rectum	200	31	16	9.4	19	36	21.3	[1] 64
Hemorrhoids	200	13	22	12	24	33	17.6	39

	Number of relatives		Relatives over 45 with carcinoma of stomach	
	Under 45	Over 45	Number	Percent
Carcinoma of stomach	888	827	16	1.90
Gall-bladder disease (noncancerous)	318	337	3	.89
Hernia	467	281	2	.79

[1] 8 percent had carcinoma of the colon.

of the stomach are probably more likely to be aware of the same disease in other members of the family than would patients who have been admitted to the hospital for other diseases. Denk (*18*) has also shown that gastric cancer appears to be more frequent in the relatives of patients with gastric cancer than in relatives of individuals of similar age groups not having gastric carcinoma.

The response that we have obtained from requesting relatives of patients with gastric carcinoma to appear for examination, even though we volunteered to carry out these studies without cost to the individual, was disappointing, for only 40 relatives of 20 patients have taken advantage of this service. Why so few people have appeared for this study is difficult to understand. It may be due to (1) lack of appreciation of the significance of the disease, or (2) to mortal fear of having cancer discovered. Certainly further intensive education of the public concerning the importance of the problem of gastric cancer is a crying need.

Occult Blood in the Stools and "Unsuspected" Anemia

No definite conclusions can be drawn from this study to date with regard to the value of using the presence of occult blood in the stool and or a hemoglobin level of 11.0 gm. or less as indicators of unsuspected gastric cancers. The former would appear rationally to afford more hope than the latter, for there are many pathologic states other than gastric cancer that are capable of producing unexplained anemia.

In addition to continuing the studies just described, it is planned to investigate patients with atrophy of the lingual mucosa and/or severe pyorrhea alveolaris as potential developers of gastric carcinoma. The former group was proposed for study because of the well-known association of lingual atrophy and pernicious anemia, and it was felt that information should be obtained on the character of lingual mucosa in cases of gastric carcinoma.

SUMMARY AND CONCLUSIONS

Further improvement in the end results of gastric carcinoma can be expected only from earlier diagnosis of this lesion. To this end, an attempt is being made to determine likely precursors of gastric cancer. They include (1) patients over 50[3] with histamine achlorhydria and hypochlorhydria, (2) patients with gastric polyp, (3) patients with pernicious anemia, and (4) relatives of patients with gastric carcinoma.

From July 1, 1945, to November 1, 1946, 1,253 patients over the age of 50 have had gastric analyses. Two hundred thirty-eight were achlorhydric to 3 successive 0.5-mg. doses of histamine; 67 were achlorhydric to 2 consecutive 0.5-mg. doses of histamine; and 45 were achlorhydric to one 0.5-mg. dose of histamine. An additional 20 patients were found to be hypochlorhydric (less than 20 degrees of free acid) after 3 consecutive 0.5-mg. doses of histamine. In these groups 2 unsuspected carcinomas of the stomach, confirmed at operation, and 10 patients with gastric polyps were discovered. A third carcinoma of the stomach failed to be identified through a misinterpretation of the roentgenograms of the stomach.

In a group of 84 achlorhydric individuals obtained from a previous study by Wetherby (*6*), 5 additional patients with gastric polyps were found.

In addition to the 15 patients with gastric polyp, discovered during the study, an additional 58 obtained from the hospital records (1938 to November 1946) have been placed under observation. To date, in 12 instances the polyp has been excised either locally (3 times) or by gastric resection (9 times).

Seventy-nine patients with pernicious anemia have been examined roentgenographically, but no gastric carcinomas were found in this group.

Gastric carcinoma appears to occur more frequently in the relatives of patients with gastric carcinoma than in relatives of patients with noncancerous, gall-bladder disease, hemorrhoids, rectal carcinoma, and hernia, although these differences were not sufficiently great to be statistically significant. Forty relatives of twenty patients have been examined. No gastric lesions have been found. The unsatisfactory response of relatives to our request for examinations indicates that an active program of cancer education for the public is urgently needed.

Of 40 patients observed in the clinic since July 1, 1946, with occult blood in the stool, 34 were submitted to X-ray examinations, no unsuspected gastric cancer being found. Of 20 patients with hemoglobin values below 11.0 gm., 10 had roentgenograms of the stomach, but none of these had unsuspected gastric carcinoma.

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GASTRIC CARCINOMA; CAN AN INCREASED DIAGNOSTIC ACCURACY GREATLY IMPROVE SURVIVAL RATES?

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Only 1 to 5 percent of the individuals with gastric cancer stand a chance of living for 5 years or more. Fifteen to thirty-two percent of the patients having a resectable carcinoma have a chance of living for at least 5 years after their operation. The majority of the patients who fail to survive die from metastases or local recurrence and not from other causes. It is stated that from 75 to 80 percent of the patients with gastric cancer have distant metastases when examined post mortem and that only 10 percent of the patients seen at surgery are free from any metastases. Although more can be accomplished in gastric surgery in the present decade than has been accomplished in the past 60 years of surgical activity, any spectacular improvement in the survival rates lies in finding the lesion before it is beyond resectability and before distant metastases occur.

This paper reviews current opinions which are offered to explain the low survival rate. The opinions, oft expressed in the literature, indicate that the patient is at fault for not presenting himself to the clinician in the earliest stage of his symptoms, that the clinician is at fault for not recognizing the symptoms and not asking for an objective form of diagnosis, and that the roentgenologist is at fault for not recognizing the lesion in its resectable stage. Admittedly, each of the principals makes mistakes, but are these mistakes great enough, if eliminated, to influence appreciably the statistics of survival, when successful surgery is carried out? In other words, do the majority of the gastric carcinomas cause symptoms or gross pathologic-physiologic or anatomic changes which can be recognized before they give rise to distant metastases?

It is not likely that improved operative mortality rates or improved surgical techniques will increase the rate of survival greatly. St. John, Swenson, and Harvey (*1*) state that although the mortality rates from surgery are lower and wider excision gets all the local metastases, the great majority of the patients are beyond hope at the time of surgery.

Current experience has established careful roentgenologic examination as the most important single diagnostic aid. Other objective methods, such as gastroscopy and exploratory laparotomy, have increased the diagnostic accuracy only slightly. At present, then, the burden of any increased accuracy in diagnosis lies with the physician who first sees the patient and the roentgenologist who examines the patient.

In view of the evidence given, the problem resolves itself into studying methods of increasing the number of patients who reach the surgeon in a resectable stage.

Time could be spent in education by describing the technique of roentgenologic examination and the appearance of small carcinomas. It is not proved that the number of patients sent to the surgeon with a resectable carcinoma can be greatly increased by increasing the diagnostic accuracy. For instance, in the Seattle Marine Hospital 89 cases of gastric carcinoma were seen, and of these 89 only 12 were of the resectable type. Of these 12, only 6 of the lesions were diagnosed at a routine roentgenologic examination by competent men not using the more improved methods of examination. If all the lesions had been diagnosed correctly by X-ray, the percentage of the total number of patients brought to surgery would not be increased greatly when compared with the entire group of 89.

There are unknown factors which cannot be estimated. How many patients with carcinoma escaped the clinician as well as the roentgenologist? Would a method of mass survey greatly increase the number of resectable lesions? St. John, Swenson, and Harvey (*1*) examined 2,432 patients, from 35 to 80 years of age and without significant gastric complaints, by fluoroscoping the patients in only the standing position without making films. In this group they found only 3 lesions, 2 carcinomas and 1 lymphosarcoma, or an incidence of 1.24 in each thousand. One might partially attribute the small figure to their method of examination. However, these authors reexamined 490 of the patients a year or so later without finding a lesion. This would indicate that the examinations were reasonably accurate.

From 1934 to 1943 I worked in close cooperation with the clinician, Dr. Walter L. Palmer, and the gastroscopist, Dr. Rudolph Schindler, and had at my disposal an improved spot machine designed for making films of the mucosal relief and of the barium-distended stomach under varying degrees of compression. Since the roentgenologic diagnosis using the spot machine has proved superior in the diagnosis of other gastric and duodenal lesions, particularly peptic ulcer, there is good reason to believe that its widespread use should increase the accuracy of diagnosing neoplasms. Although the gastroscopist found a few lesions which were not observed by the roentgenologist, and the clinician sent to the surgeon a few patients, in whom the gastroscopic and roentgenologic changes were nebulous, the results were disappointing when viewed in the light of markedly improving the possibilities for cure. Although I do not have the figures available, one of the surgeons, Dr. Alex-

ander Brunschwig, who is a member of this group, expressed the opinion that very few patients came to surgery in a stage more resectable than before the study was begun. During the war, when clinicians, unable to do exhaustive clinical work-ups because of the shortage of physicians and overloaded schedules, relied largely on roentgenologic surveys of the gastrointestinal tract, approximately 20,000 examinations of the stomach were performed. Here again, I do not have the exact figures, but the number of patients having unsuspected gastric cancer were very few.

Although the evidence tends to condemn objective forms of diagnosis as aids in appreciably decreasing the mortality rate by bringing the patients to the surgeon in a stage in which metastases have not yet occurred, the method cannot yet be discarded. In the first place, a small percent of the patients are salvaged. In the second place, what is the expectancy of a case-finding program? Engel (*2*) stated that the death rate is 29.6 per 100,000, or approximately 0.3 per 1,000. He did not state the age groups. Hoffman (*3*) drawing on life insurance statistics from over the world, found that the death rate when related to all ages was 27.5 per 100,000. When he broke the figures down, he found that the incidence for each 100,000 was 56.6 for the ages between 45 and 54; 138.5 between 55 and 64; 231.8 between 65 and 74; and 255.4 over the age of 75. The average for the ages of 45 and over was 120.5 per 100,000 or 1.20 per 1,000. Livingston and Pack (*4*) stated that about 95 percent of the patients with gastric cancer live not more than 2 years. From these figures it is possible to state that the number of individuals who have gastric cancer and who are over the age of 45 is less than twice yearly mortality rate, or between 1.2 and 2.4 per 1,000. The figure does not differ greatly from the 1.24 found in the survey of St. John and his colleagues and would seem small to anyone conducting a mass case-finding program.

Should a more exhaustive case-finding program on patients without digestive signs of appreciable significance, such as was conducted by St. John, Swenson, and Harvey, be done on a much larger scale and should it prove highly accurate in segregating those patients with carcinoma, it still would not prove that an increased accuracy in diagnosis would increase the survival rate. There are still unknown factors. It is not known how the majority of carcinomas grow or whether they could be detected before they give rise to metastases. Until these phases of the problem are solved, we cannot raise our hopes too much that any increased accuracy in diagnosis, using our present methods, will increase greatly the number of patients who survive 5 years after surgery.

The paragraph with which St. John and his colleagues close their paper is very apt. They write:

> Whether this method (case-finding) is a practical one for reducing the large number of incurable gastric carcinomas that come to our hospitals, we cannot say. At least one thing should come out of it, if nothing else, and that is an opportunity to learn more about the characteristics of early gastric carcinoma, for our experience so far has, unfortunately, been chiefly with its late manifestations.

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BIOLOGIC CHARACTERISTICS OF NONPALPABLE, NONSYMPTOMATIC, SOLITARY POLYPS OF THE RECTUM

By MARIE ORTMAYER, M. D., *Women and Children's Hospital, Chicago*

The source material for this study is based upon the sigmoidoscopic examination of well women who presented themselves for complete examination in the Cancer Prevention Center of Chicago, directed by Dr. Augusta Webster and Mrs. Arthur Edison. The aim of this clinic is to find cancer early. Between April 1945 and November 1946, 1,031 of these women elected to have sigmoidoscopic and roentgenologic examinations of the colon. The National Cancer Institute and the National Advisory Cancer Council, under Drs. Thomas Parran, R. R. Spencer, and George M. Smith, provided the grant (No. 224) to Dr. Marie Connelly, roentgenologist, and the speaker to cover the basic costs of the special examinations.

The ages of the 1,031 women ranged from 22 to 73 years; two-thirds of them were between 31 and 56 years old, and nearly three-fifths between 36 and 47 years old. The youngest woman with a polyp was 26, the oldest 61.

In addition to ordinary history taking, a special symptomatic inquiry was made in this group. Ten symptoms and signs, which may be present in advanced rectal or colonic new growth, were listed:

(1) Rectal bleeding;
(2) Rectal discharge other than bleeding;
(3) Change in bowel function in past year;
(4) Pain in relation to defecation;
(5) Rectal, sacral, or abdominal pain, unrelated to defecation;
(6) Loss of weight in past year (over 3 pounds);
(7) Vomiting;
(8) Weakness;
(9) Hemorrhoids;
(10) Abdominal masses.

Although these 1,031 women considered themselves well (many had waited 6 months for their appointments), when directly questioned three-fourths of them complained of specific symptoms (25 percent of 1 of these symptoms, 22 percent of 2, 14 percent of 3, and 12 percent of a multiplicity of them), leaving only about one-fourth of the total number free from complaints of any kind. Two of the women in whom we found solitary rectal polyps had no complaints. The remaining 16 with polyps had either 1 or 2 or a multiplicity of specific complaints, which were not due to the polyps, because the latter were too small to cause symptoms other than perhaps occasional bleeding.

During the inquiry concerning the presence of cancer in relatives, the specific locations in organs were usually not obtainable, but the presence of cancer in father or father's family, mother or mother's family, or both father's and mother's family was positive in 45 percent of the total women. In the 18 polyp-bearing and 1,013 non-polyp-bearing women, there was no distinctive difference in the family incidence of cancer which might have guided us in the selection of women for proctoscopy.

In our study, we found no combination of symptoms and signs common to carriers of rectal polyps which were not shared by the noncarriers. We have no proof at present that the initial phases of these polyps, as is true for carcinogenesis in general, are associated with specific changes elsewhere in the body which could draw the physician's attention to them. Routine proctoscopy alone revealed polyps in these 18 women.

I have omitted from this paper the report on the anal polyps found by us. These polyps do not require proctoscopy; they are either seen externally, or they are felt in the anal ring and are readily delivered externally. They are covered by stratified epithelium and rarely, if ever, become malignant.

For purposes of this report, I speak of the rectum as that portion of the distal colon which lies above the anal papillae and can be reached by the 25-cm. sigmoidoscope of 8 mm. diameter. This includes the rectosigmoid and lowest portion of the sigmoid colon, as these are defined by anatomists and anatomically minded proctologists. The location of the juncture between rectum and sigmoid varies and has no exact landmark, and therefore it is simpler for the proctoscopist to describe the location of lesions seen by distance on the proctoscope from the external anal ring, mentioning the usual knee-chest or any variation of position taken by the patient while being proctoscoped. (Ours were all done in the knee-chest position.) Two assistant physicians performed the original sigmoidoscopies. Those patients in whom polyps or other abnormalities were found were referred to the speaker for recheck proctoscopy and biopsy. Heights of 21–25 cm. from the external anal ring were reached in 80 percent of all women examined; and polyps of the smallest dimensions were accurately located, so that they could readily be found at subsequent proctoscopies. Less uniform was the record of the position of the polyps on the bowel wall according to clock dial. With experience, even the latter became more accurate.

In this study, 19 rectal polyps were found in 18 women, 2 in 1 patient. None of the 19 were palpable by rectal examination, even after we knew they were present. None were seen at barium enema or on the contrast X-ray film. The largest of the tumors was a centimeter in each direction, the smallest estimated at under 2 mm. Ten were

under 6 mm. in all directions. Only 4 of the polyps were pedunculated. The remainder were sessile.

The color of 13 of the polyps was that of the surrounding mucosa, which in all 18 patients was normal and not inflamed. Two polyps were described as pink-white, 2 as fleshy red, 2 as deep red. All but one were soft. The firm one (one of the largest, seen at 15–16 cm. height) slipped away from the biopsy forceps repeatedly and looked grossly malignant but was found to be histologically benign, not only on biopsy but also on subsequent complete removal. Another large one, of similar size, was covered with epithelium the color of the surrounding mucosa and did not look malignant but was histologically carcinomatous.

Eleven of these polyps were found at a distance between 11 and 15 cm. from the external anal ring, 9 almost exactly at 13 cm. Of the remaining 8, 4 were found at 9 to 10 cm. and 4 at 16 to 18 cm., which is close to the rectosigmoid juncture. None of the rectal polyps were found below the 9-cm. level, and none above 18 cm. As the sigmoidoscope reached the height of 22 cm. or over in 17 of the 18 women in whom polyps were found, the incidence at the heights just given is not due to limitations of the proctoscopic method in the hands of inexperienced physicians or of failures to reach higher points due to bowel fixation or spasm.

Grossly most of our polyps looked benign. Eleven were found on the posterior half of the bowel wall. Other physicians listing far greater numbers of solitary polyps have found the anterior wall most frequently involved.

Contrary to the common present practice of some proctologists, a biopsy was taken from each of the 19 polyps. In a few instances, the biopsy included the whole very small polyp.

The stained slides were examined by 3 Chicago pathologists of distinction independently of each other. I am greatly indebted to them for their willingness to cooperate in this manner. Their histologic reports are challenging. Classifying on the basis of benign, suspicious (called precancerous by some pathologists), and carcinomatous, all 3 agreed in diagnosis on only 3 of the slides made from the biopsies. Of these 3, 1 was malignant and 2 were benign. There was total disagreement on 6 of the biopsies. Each of the 6 was called by one pathologist benign, suspicious by another, and malignant by the third pathologist. This leaves 10 polyp biopsies in which the combined opinions ended 2 to 1; 8 of these 10 were pronounced benign by 2 pathologists and 2 suspicious. This difference of opinion should not be too confusing to the clinician, or discouraging. It may initiate an important discussion on rectal polyps such as occurred when preinvasive carcinoma (also called surface carcinoma and carcinoma in situ) was first diagnosed in the cervix uteri. It is similar to a discussion still going on between the urologist and pathologist in regard to bladder polyp malignancy or benignity. It concerns all growths that begin as surface growths and remain so for some time. It is related to the question, What are the earliest epithelial-cell changes of carcinoma when growth becomes unrestrained, when cells crowd each other, when nuclei change their morphology and position in the cells, when cytoplasm changes its chemical reaction with staining dyes, and when normal production of mucus in the rectal epithelium disappears? To my knowledge, in this country, the pathologist, Dr. Walter Schiller, first spoke of these possible early carcinomatous changes in rectal polyps at a meeting of the National Proctologic Association in 1941 in Chicago.[1] He emphasized that the cytoplasm of the carcinoma cells stains darker than does the cytoplasm of the normal cells; that, as in the squamous epithelium of the uterine cervix, normal and carcinomatous glands are seen side by side without gradual transition between them, and that even within 1 gland the lining epithelium may be normal and carcinomatous in close juxtaposition.

Some slides (figs. 1–4) illustrating the problem, with normal and changed epithelial cells on the same slide, may be of interest to illustrate the present status of the quandary and the difficulty for the pathologist, who carries such a high responsibility in the diagnosis of tumor.

If these cellular changes represent beginning carcinoma in partly benign polyps, then of the 19 biopsies only 3 are totally benign, 8 are "suspicious" for carcinoma, and 8 are partly carcinomatous with benign and carcinomatous epithelium in the same slide.

None of them show invasion of mucosal connective tissue. They are either preinvasive stages of carcinoma or denote cellular changes due to unknown causes other than carcinoma. In figure 4, there is as yet no invasion of connective tissue by carcinomatous cells, but all three pathologists agreed that this is malignancy in a rectal polyp. At present no known tissue culture can separate these abnormal from normal cells, nor do we have a chemical "marker," which injected in vivo will differentiate a carcinoma cell from normal rectal epithelial cells and from otherwise changed cells.

[1] See note by Dr. Schiller, following the present paper.

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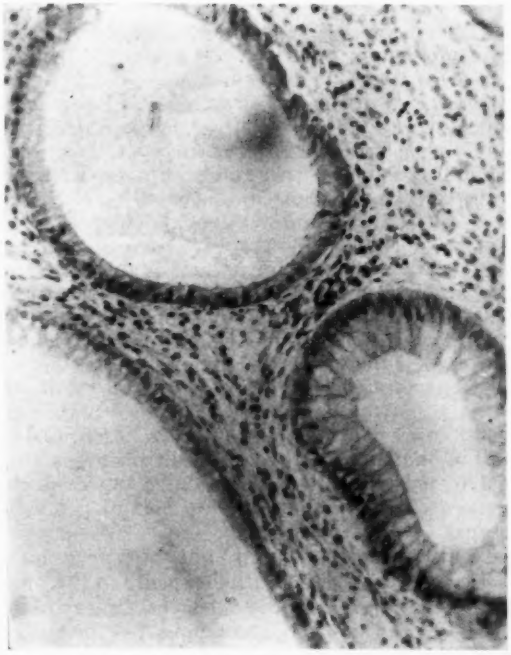

FIGURE 1.—Patient No. 756. Biopsy illustrating the totally benign epithelium, though flattened, in cystically dilated glands. In the gland with columnar epithelium, there is mucin production in the cells and the nuclei are basal. In hematoxylin and eosin stain, the cytoplasm is of normal color.

The treatment to date recommended by us whenever consulted for these small tumors, whether carcinomatous or not, has been electrofulguration, since we know that frank and much larger carcinomas have been successfully treated in this manner when the base has been thoroughly and deeply fulgurated. Benign polyps have long been so treated to avoid the later so-called transformation into malignancy. It does not take too much courage, if preinvasive carcinoma is diagnosed in a tiny rectal polyp, to recommend eradication by means other than radical resection or sleeve resection of a segment of the rectum. Tying or cutting or twisting off a polyp with long, thin, noninvaded pedicle should accomplish the same result. Radium needles should be effective. I have observed the surgical removal from the sigmoid by excision around the base, of a pedunculated truly carcinomatous polyp with excellent result to the patient and a 5-year survival to date.

Such surgical excision is difficult to do in the rectum, and this is the reason for resorting to biopsy and fulguration. Two of our polyps, removed in their entirety by biopsy forceps in December 1945, without fulguration of the base, have not recurred. The diagnosis on both was suspicious for carcinoma.

The number of single rectal polyps reported in this study is small, and the follow-up period at longest is a year. No absolute conclusions are justified, but certain aspects of this subject need emphasis:

(1) Among well women between the ages of 22 and 73 years, nearly 2 percent at proctoscopy will be found to harbor polyps in the rectum above the anal papillae, some of which will be benign, some suspicious of early carcinoma, and some diagnosable as preinvasive carcinoma (also called surface carcinoma or carcinoma in situ). For the time being, pathologists vary widely in their interpretations of the histologic preparations.

(2) As has been frequently stated in the literature of the past, routine proctoscopy repeated at 6- to 12-month intervals in well persons, with or without complaints referable to the colon, will reveal tumors of small size when they are most amenable to the simpler methods of removal. History taking is of little value to determine if early tumor is present. Effectiveness of the digital

FIGURE 2.—Patient No. 386. Biopsy, showing changes "suspicious" of carcinoma ("precarcinomatous"). These changes are visible in the same gland (at *X* and *Y*). Partly normal mucus-secreting columnar epithelium, in sharp juxtaposition to crowded cells with cytoplasm more basophilic than normal. The nuclei are still fairly normal and basal in position.

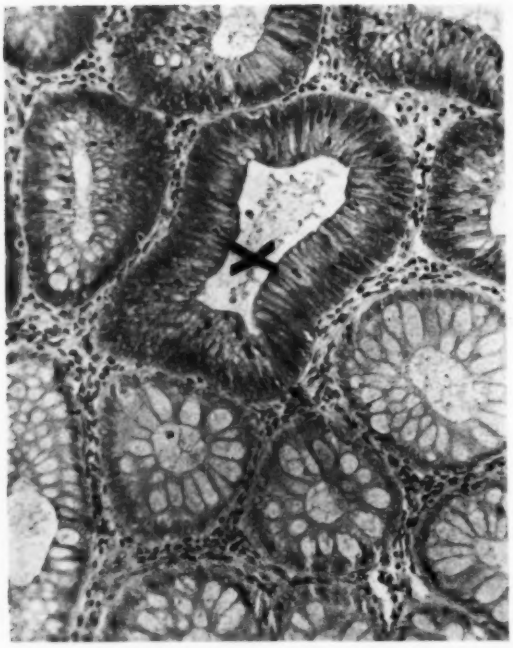

FIGURE 3.—Patient No. 687. Biopsy illustrating the sharp distinction between normal mucin-secreting glands and the glands, especially at X, which shows the changes in cellular structure suggestive of early carcinoma. Cells crowd each other, the nuclei are flattened and tend to rise from the basal position, and the cytoplasm is more basophilic than the normal in hematoxylin and eosin stains.

rectal examination has been overrated in the detection of beginning tumor.

(3) Dextrous, well-taught, young physicians are suitable for conducting routine proctoscopies. One cannot be dependent on the highly trained proctologist for picking up early lesions in the total adult population.

(4) Patients must be adequately prepared. The mucosa must not be smeared with irremovable stool or mucoid secretions which hide the smallest of these lesions. So-called well patients are not inconvenienced too greatly by the castor-oil technique, which we have adapted from Weber's preparation for barium enema and which yields clear vision in a high proportion of patients. A thorough enema preparation is less generally useful in our experience.

(5) It is urgent, contrary to the present practice in treating small rectal polyps, to take biopsies or to remove the polyps totally by other methods than fulguration, because the latter destroys the cellular characteristics. Pathologists need to review this whole subject of bowel polyps in the light of advancing knowledge of early cellular changes in carcinoma. At present we are hopelessly confused by their terms of "metaplastic," "hyperplastic," "pseudoadenomatous," "papillomatous," "benign," "precancerous," and "carcinomatous" polyps, "carcinomas," and "benign adenomas." I personally believe that it is only by close cooperation of the clinician, pathologist, and therapist that we shall solve the problem of rectal new growths in human beings. The clinician should be willing to leave in place the truly benign polyp and even the suspicious polyp. Follow-up by frequent proctoscopy and repeated biopsy, at suitable intervals, and simpler methods of therapy for the preinvasive carcinomas with frequent proctoscopic follow-up can be the clinician's and patient's contribution, and they with the pathologist can help to solve the problem of cancer genesis in the bowel. Other important questions, such as whether the rectal carcinoma begins in the tip, stem, or side wall of the polyp, or even in multiple areas adjacent to the polyp, could be decided by reasonable cooperation without inordinate fear of cancer on the part of any of us.

To justify a place for this paper on a program on gastric cancer, I should allude briefly to the problem of small lesions of the stomach. X-ray examination of the stomach, much more readily than is

FIGURE 4.—Patient No. 513. Biopsy showing malignancy. Cells crowd each other, cytoplasm changes reaction, and nuclei are larger, rising out of position. One mitotic figure may be seen.

the case of rectum and colon, picks up tumors of over a centimeter in diameter, due to the pliability of the stomach, its accessibility to the palpating hand, and compression technique. For the detection of lesions in the stomach of size similar to those reported herein, i. e., 1 cm. or under, gastroscopy is the only method, but it is a far more difficult technique than proctoscopy. It is also harder on the patient and therefore less suited to be offered as a routine. Gastroscopic "blind spots," sometimes very large on the posterior wall and greater curvature and even antral lesser curvature, interfere with complete survey of the gastric cavity. A safe, suitable biopsy forceps for use with the gastroscope has not been developed. At present some of these handicaps seem insurmountable.

In closing, let me say that only further careful study of rectal polyps, with full cooperation between clinician, pathologist, therapist, and patient, will eventually solve some of the problems raised by this report.

CRITERIA FOR THE DIAGNOSIS OF MALIGNANCY IN RECTAL POLYPS[1]

By WALTER SCHILLER, M. D., *Women and Children's Hospital, Chicago.*

The great difficulty in comparing or combining statistics published by various authors on the malignancy of rectal polyps lies in the fact that different criteria are used by different authors in diagnosing malignancy. Changes which one investigator accepts as sufficient for classification of the case as full-fledged carcinoma are accepted by a second pathologist only as evidence of a suspicious case, whereas a third voluntarily or involuntarily overlooks the changes and registers the case as negative. If each author publishing a statistic would add a brief definition of his concept of malignancy and of the criteria which he used for the classification which served as the basis for his statistics, it would be possible to avoid comparison or combination of statistics based on contradictory criteria. It might then be possible to transform statistics to bring them to a common denominator.

For the classification of Dr. Ortmayer's cases, criteria were used as presented and discussed in an address delivered in the symposium on rectal carcinoma, September 24, 1941, at the Eighteenth Annual Convention of the National Proctologic Association in Chicago.

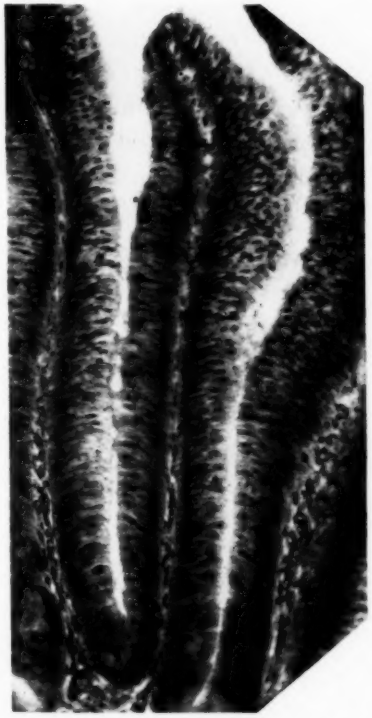

FIGURE 1.—Glands with carcinomatous epithelium.

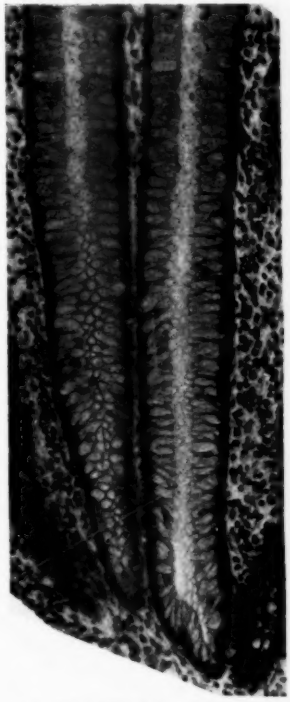

FIGURE 2.—Glands with normal epithelium.

Small initial carcinomas of the rectum, as well as those in the borderline zone of progressed carcinomas, frequently present pictures which duplicate in some regard the first stages of carcinoma of the squamous epithelium of the uterine cervix. The carcinoma starts by forming a preinvasive carcinoma in situ. It is characterized by primary transformation of the regular normal epithelium, with its columnar cells with light-staining protoplasm and relatively small nuclei located in one row at the base of the cells, into narrow but higher cells of violet-staining protoplasm and larger nuclei located higher in the cells (fig. 1, 2), and later in the piling up of the cells into two or even three rows, which together are not much higher than the one row of normal cells. Normal epithelium may be interspersed with goblet cells, which are in general missing in carcinomatous epithelium. The change of epithelium first occurs without change of general structure and architecture of

[1] Included at the request of Dr. Marie Ortmayer, to supplement her paper.

the mucosa. Later its pictures correspond to the glandular and cystic type carcinomas of high maturity of the endometrium, formerly classified as adenoma malignuma (fig. 3). The transformation from normal to carcinomatous epithelium in general occurs without intermediate phases: the dislocation of the nuclei only may be preceded by the darker staining of the protoplasm. Frequently normal glands are seen next to carcinomatous glands (fig. 4). Sometimes the lining of one gland consists of normal and of carcinomatous epithelium separated by a sharp borderline with no transitional cells between the last normal and the first carcinomatous cell (fig. 5).

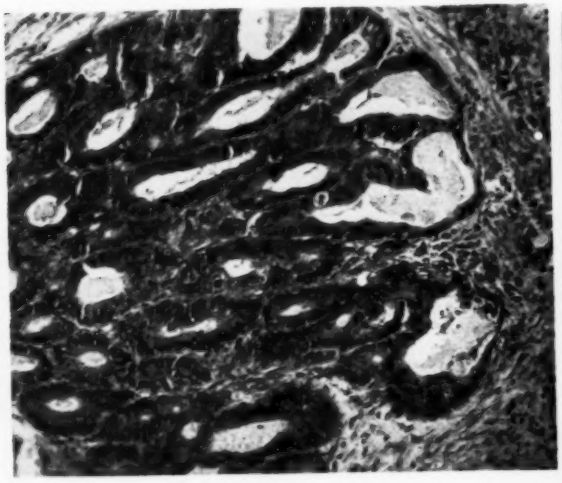

FIGURE 3.—Glandular and cystic carcinoma duplicating by its structure the "adenoma malignum" of the endometrium.

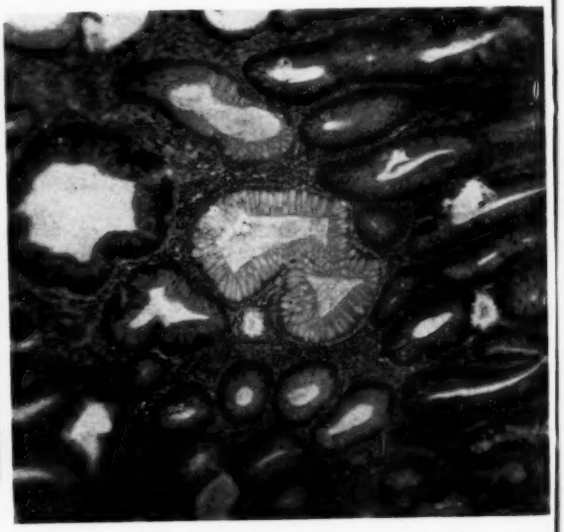

FIGURE 4.—Normal glands surrounded by carcinomatous glands.

FIGURE 5.—Carcinomatous gland, the upper part of the left wall lined with normal epithelium.

Chairman Ivy: The papers presented today are now open for discussion. I should like personally to urge everyone who is particularly interested in the detection program to be present tomorrow morning, because detection is one of the important items to be considered in the program on the control of cancer, whether or not it is even worth while for the purpose of collecting more evidence. Dr. Templeton's paper gave some of the points that must be considered.

Dr. Lushbaugh: I want to ask Dr. Strong if as yet any of his mice are available for study in other laboratories.

Dr. Strong: Every time I talk about these mice that give rise to gastric cancer, I lose a friend, since everyone wants them. The last time Dr. Gye, of London, was in this country, I gave him the statement that I have just made. He looked at the microscope and said, "I don't blame you. But when you begin to pass them out, will you give me some?"

The situation is this: These are highly hybridized mice in which biologic variability is not only taking place spontaneously, but also the germ plasm is being bombarded by a very powerful cancer-producing substance, methylcholanthrene. In other words, quantitative research cannot be done on these mice at the present time, and it would be unwise for a geneticist who employs quantitative research to recommend that these mice be used in other laboratories. When the latent period becomes stabilized so that quantitative results can be obtained not only in genetics but also in studies of nutrition, enzymes, or what have you, then these mice will be available to anybody who desires to use them for cancer research.

Chairman Ivy: Am I correct, Dr. Strong, in assuming that another mutation of the type you reported this morning might occur and that that possibility would have to be considered in interpreting results?

Dr. Strong: That is what I mean by quantitative research. Reproducible results are not so readily obtained as they may be in the investigation of bronchiogenic carcinomas. Anybody who uses the old established inbred strains such as the A or the C3H will get the same percentage incidence of cancer at the same age, because everything in the experimental material is fixed or static. At present the biologic nature of these new NHO mice changes from time to time, and therefore reproducible results cannot be expected under different environmental conditions.

Dr. Brunschwig: I should like to ask Dr. Strong if he has had an opportunity to make chemical analysis of the gastric secretion of these mice.

Dr. Strong: I reported that these mice have a reduced total acidity of the gastric contents. I also reported that there is reduction of circulating hemoglobin which is more pronounced in gastric carcinomas than in bronchiogenic carcinomas of the same degree of malignancy, but it is less pronounced than it is in leukemia. There is variation of total gastric acidity. Some of the mice had a complete achlorhydria and an anacidity. For gastric contents of mice, you cannot make a free hydrochloric acid determination with the technique that I employed. The Topfer reagent is entirely unsatisfactory in determinations of acidity in the gastric contents of mice when you have to be satisfied with one twelve-hundredth of a cubic centimeter. My determinations therefore are on total acidity and not on free hydrochloric acid.

Dr. Morris K. Barrett (National Cancer Institute): I want to ask about the same mice (i. e., Strong's), but I think I should ask the question of Dr. Warren. Have you seen in the slides of Dr. Strong's mice evidence of atrophic gastritis or similar associated processes?

Dr. Warren: At times we see areas adjacent to the polypoid lesions where there is cystic degeneration, areas where there is lymphoid infiltration, areas where there is alteration of the epithelium in the way of "decreased differentiation," a term that I prefer to "intestinal metaplasia."

Dr. Kaplan: On this question of gastric acidity in the NHO strain of mice, I might add some information. Dr. Strong was kind enough to let me use some of these mice for some gastric-acidity studies, and we were interested in determining whether chronically produced hyperacidity might influence the incidence of these gastric tumors. Before starting on such an experiment, it was important to determine whether the agents ordinarily used to produce gastric secretion would have any effect on these mice.

Accordingly, we tried to work out a technique for tying off the pylorus of these mice, injecting an agent such as histamine, and subsequently aspirating the gastric secretion and titrating. We were rather surprised to find, in experiments which are as yet incomplete, that histamine apparently has absolutely no effect on gastric acidity in the mouse and that controls which received no histamine whatsoever had free acid in amounts and frequency comparable with those of the animals receiving the drug.

Similarly, caffeine seems to have no effect on gastric acidity in the mice that we have studied. The only drug that has given any promise of producing a gastric secretory response in respect to free hydrochloric acid is a drug related to choline, one that has been called "Doryl" in the English literature and is known here as "carbamyl-choline" (Merck).

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Dr. F. H. J. Figge (University of Maryland Medical School): I should like to make some comments at this point on the terminology being used in this conference with regard to the acidity of gastric contents. It seems to me that the terms "hyperchlorhydria," "hypochlorhydria," and "achlorhydria" are somewhat antiquated and not quantitative. We should be using terms that have some regard for hydrogen-ion concentration expressed specifically in terms of pH. From studies on the permeability of gastric mucus to porphyrins and carcinogenic agents, we have derived some evidence that the pH may be the important factor in the etiology of cancer of the stomach. At pH 3, the approximate isoelectric point of gastric mucin, a great many substances permeate the gastric mucus and penetrate to the mucosa. At this specific pH, the mucous coat loses its protective-barrier function. I therefore suggest that in the future investigators attempt to determine and express gastric acidity in terms of pH values. Even with mice this should be simple, for there are available today pH papers that merely have to be wet with this gastric material, to determine the pH fairly accurately.

I also cannot help but inject at this point— and it may seem irrelevant to those of you who do not know me, but not so irrelevant to those of you who do—the fact that in pernicious anemia there is a high urinary excretion of porphyrin, and this is one of the abnormal findings that should be investigated as a possible factor in the genesis of gastric cancer.

Dr. Walter L. Palmer (University of Chicago): I don't like to discourage the last speaker, but some years ago we did study the pH of gastric secretion in patients with gastric cancer, and in the main I think they parallel the free acid.

I should like to make a few comments with regard to the matter of early diagnosis.

The outlook for early diagnosis, really early diagnosis, is pretty pessimistic. However, Dr. Maimon, in a review of cases seen at the University of Chicago clinics in the last 15 years, did obtain some fairly definite evidence that diagnosis had been made a little earlier in the last 5 years than in preceding years. This may be a matter of improved economic condition of the people, or a matter of education among the laity, or more particularly, I suspect, of education of the doctors.

In that connection, I should like to suggest that while it is very worth while, perhaps, to look for screening methods that will enable us to detect the patients in whom gastric cancer may be demonstrated, it would be more worth while to X-ray all patients with dyspepsia. Doctors do not routinely send to the roentgenologist for study all patients with dyspepsia coming into their offices. There are many reasons for their failure to do so. The great majority of patients with dyspepsia do not have gastric cancer but a functional dyspepsia which subsides after a few weeks, regardless of treatment.

It is rather difficult to get doctors interested in gastric cancer. The general practitioner doesn't seem to see enough of it, or he has a very pessimistic attitude towards it. Of course, that pessimistic attitude is supported by the figures which Dr. Pack showed this morning. But on the other hand, there is evidence, as Dr. Pack pointed out, that in the last 5 or 10 years prognosis has become a good deal better than it was, and that perhaps in the next 10 years prognosis will improve still more.

I should like to ask Dr. Strong, and perhaps Dr. Warren would speak on this, whether there is a marked variation in the degree of malignancy in the tumors in different animals. I was going to ask if the degree of malignancy depended on the dosage of the carcinogenic agent, but I deduce from your earlier remarks that you aren't able to speak in such quantitative terms. Is it a matter of the age of the animal, or is there any relationship between the length of the latent period and malignancy of the tumor finally developed?

Dr. Strong: I shall answer that as a geneticist and then Dr. Warren may answer as a pathologist.

When one investigates these tumors not only of the stomach but of the bronchiogenic carcinomas, the scirrhous carcinomas of the mammary gland, carcinomas of the liver, and various other carcinomas in this series of hybrid mice in which biologic variability has been increased considerably by hybridization, there is only one conclusion to be reached, namely, that this variation in the types of tumors produced is due to the variation in the biologic nature of the mice themselves. Inbred mice in which the degree of inbreeding has been considerably increased over, let us say, a hundred generations, by brother-and-sister matings, give rise to very few types of relatively benign tumors. When this biologic variability is increased by hybridization, a tremendous variation in the types of tumors is encountered.

All these mice received the same experimental treatment, 1 mg. of methylcholanthrene dissolved in 0.1 cc. of sesame oil at 60 days of age.

Dr. Warren: I don't think I can add anything from a pathologic standpoint.

Dr. George Wakerlin (University of Illinois): I should like to ask Dr. Papanicolaou how many of his patients showing carcinoma cells in the gastric fluid were operable and how many were late.

Dr. Papanicolaou: I believe that my associate, Dr. Cooper, could answer that question better.

Dr. Cooper (New York Hospital): They were just half and half, half of them were operable and half inoperable. Two of them were what you might call very early cancers. They were cancers that looked clinically like ulcers.

Chairman Ivy: On how many do you have records regarding the relation of the onset of symptoms to the time of the diagnosis?

Dr. Cooper: I have not that information at my finger tips.

Dr. H. L. Stewart (National Cancer Institute): I was very much interested in Dr. McPeak and Dr. Warren's presentation of this gastric lesion which Dr. Strong finds in his mice. I saw some of these sections in 1942 or 1943, and, as I recall, at that time I said that some of them might possibly be cancer although it was very difficult to tell. It is one of those things where it is very difficult to rule out the possibility of cancer from examination of a single slide.

In the stomachs of the strain I mice when we first began looking at them, we were up against the same proposition. We found, for example, this inordinate overgrowth of the gastric mucosa with the cellular atypism which is shown to exist in strain I mice, and in addition the same tendency for this altered mucosa to poke down through the gastric wall, not quite through, however, although when one first looked at the slide, it looked like infiltration. However, careful study of those sections revealed that the fragment of mucosa when found deeply placed was always covered by stroma and very frequently by smooth muscle from the muscularis of the stomach. In some of the first cases Dr. Andervont and I examined, we found these pseudo-infiltrations even extending into the veins, and you can imagine that we thought we were dealing with true cancer. However, over the years that we have studied this lesion—and that includes a study of hundreds of strain I mice—we have never observed this lesion to undergo a definite malignant change. It never invaded the wall of the stomach over a wide area; it never metastasized. So we considered it to be not definitely malignant.

Now, from looking at the illustrations which Dr. McPeak and Dr. Warren showed today, I can see no essential difference between the lesion we described in the strain I mice, and occasionally in some other strains, and the lesion presented this morning.

When gastric cancer is induced in mice, there is no doubt about its being cancer—it's just like cancer in man. We induced it by injecting methylcholanthrene into the walls of the stomach. We induced cancer of the glandular mucosa. There is no doubt, since they have metastasized and they have absolutely all the characteristics of cancer.

From the presentation this morning of Dr. Strong's work and particularly from the pathologic studies, I see no reason to regard this lesion as cancer. The only cancers I recognized that were presented were carcinomas of the forestomach, which of course may occur spontaneously, or the mice may possibly lick an area where methylcholanthrene was injected or painted, and it is quite possible that carcinoma of the forestomach may have been induced by that method. But I have seen nothing this morning to indicate that Dr. Strong is dealing with a primary cancer of the glandular stomach in mice.

Dr. Jacob Heiman (Columbia University): Dr. Strong, I want to ask about the site of implantation of the methylcholanthrene and whether this tumor that you have produced is transplantable subcutaneously.

Dr. Strong: I shall answer that in the negative, for the reason that as a geneticist I believe that the transplantation of tumor is no evidence of malignancy. It is an academic problem of the relationship between the tumor and the host.

I should also like to answer Dr. Stewart, that the I strain he referred to is also a strain that was developed by me, although recognition for this contribution is not usually forthcoming. This lesion in the stomach of the I mouse, however, is of broad origin involving practically all the gastric mucosa, and the hyperplastic areas grow expansively, but I have never seen a case of true invasion to the serosal surface, and I have never seen a metastasis from the lesion.

Further, there is a difference between the gastric lesion of the strain I mice and that in the NHO strain of mice, to which I referred this morning. This is a sex difference, in that the lesion in mice from the NHO strain is much more prevalent in males than in females, whereas among the I strain animals of my series there is no such difference. This is a difference biologically speaking, therefore, between the lesion that occurs spontaneously in the I mouse and the lesion referred to this morning in the NHO strain.

Chairman Ivy: Did you not show a specimen in which metastasis occurred in the parietal peritoneum?

Dr. Strong: Yes, metastases from the NHO gastric lesion have occurred into the liver, onto the diaphragm, and throughout the abdominal cavity.

Dr. Heiman: Did the tumor grow at the site of implantation of the methylcholanthrene?

Dr. Strong: That is a long story. The essential feature is this: If one increases biologic variability by hybridization and then by injection of methylcholanthrene, one expects a tumor at the site of injection. This is not always the case in the progeny. By keeping the descendants of a cancer-resistant pair of mice one can suppress that tendency to give rise to a local tumor. These mice, then, being of a hybrid nature, develop tumors all over the body, mouth, eye, ear, uterus. Some of those new-appearing types of tumors are bronchiogenic carcinomas, liposarcomas, leiomyosarcomas of the uterus, hemangiomas of the abdomen,

scirrhous and anaplastic carcinomas of the mammary gland, and anaplastic carcinoma of the liver, in addition to the gastric lesions discussed today.

Dr. Stewart: I should like to ask Dr. McPeak how many cases of adenocarcinoma of the stomach she has found in Dr. Strong's mice and whether or not she examined a microscopic section of the gastric lesion Dr. Strong showed this morning showing nodular areas on the serosa.

Dr. McPeak: I am not in a position to comment on the cases that Dr. Strong presented this morning, since we have not studied all the mice in which Dr. Strong has found gastric lesions. I believe that Dr. Strong said he had found tumors of the stomach in 5 or 6 hundred mice, whereas we have studied only 149 mice of the NHO strain and 93 mice of the F series. At present we are unable to classify the adenomatous lesions of the glandular stomach in the mice we have studied. We have presented the problem involved and hope that other studies, such as transplantation of the lesions, studies on genetic factors, enzymatic studies, and further histologic observations on the F series at different age levels, will permit us to establish histologic criteria for diagnosis of these lesions.

Dr. Strong: There is one point that hasn't been brought out, and that is, when I showed these lesions to Dr. Harry Zimmerman, he looked at the atypical cells that are found in these invasive gastric mucosal lesions, and on the basis of atypism, the bizarre-shaped cytoplasm, and so forth, he pronounced them carcinomas because bizarre-shaped cells occur only in carcinomas.

That point has not been discussed today, but whether it is a disputed point among pathologists, I cannot say. It doesn't make any difference to a geneticist what this lesion is called, particularly when diagnosed, as in some cases, by intuition. "A rose by any other name would smell as sweet."

Dr. Stewart: I should like to ask Dr. McPeak if she found any case in her series of metastatic adenocarcinoma in these mice.

Dr. McPeak: We have found no metastases from the adenomatous lesions of the glandular stomach of the NHO strain or F series of mice, though pancreas, liver, and peritoneal lymph nodes were examined in many cases. Two cases of squamous-cell carcinoma of the forestomach showed invasion of the diaphragm, liver, and pancreas by these tumors.

Dr. Wakerlin: I should like to ask Dr. Strong whether he cares to expand the possible mechanism of the overcrowding factor to which he referred. It is the first argument I have heard for the present housing shortage.

Dr. Strong: There is a very significant difference obtained in the incidence of these spontaneous tumors of mice when there is overcrowding of the mice in boxes. The mice are actually smaller in size. I believe that they eat more; they are more active; they show less disease; and they actually live longer under the overcrowding condition. Why they give rise to fewer tumors, I haven't the slightest idea. If you want to prevent adenocarcinoma of the breast in the mouse, all you have to do is to take the most susceptible strain in existence, the C3H strain, and keep 45 or 50 in a box together, and you will have very few spontaneous adenocarcinomas.

Chairman Ivy: Has the factor of fasting or undernutrition been controlled in this overcrowding?

Dr. Strong: No, they have food and water ad libitum, and their boxes are changed more frequently than they are if there are fewer in the cage.

Dr. Berkson (Mayo Clinic): Though this is hardly relevant, I can't suppress saying out loud what I was thinking to myself. Professor Strong quoted Shakespeare about the rose smelling just as sweet by any name. May I recall also that Gertrude Stein said a rose is a rose, is a rose, and that ought to settle it. And he mentioned that his animals live longer when they were more crowded. Now I used to work in the laboratory of the late Raymond Pearl, and having to do anything that he told me to do, I counted flies. I counted thousands and thousands of flies. One of the great biologic laws that came out of this vast labor was that average longevity decreased with density. We worked this all out mathematically, and it seems to me pretty mean to show at this late date that we were wrong! But the relevant question I wanted to bring up is this—it is really Dr. Barrett's question. He asked some of my colleagues, and they asked me, and I am passing it on. It comes out of some statistics we produced in my department at the Mayo Clinic some years ago because someone in the institution was writing a book. We got out all the surgical cases of carcinoma of the stomach which we had seen up to that time, punched the assorted relevant data on cards, and rolled out all the possible permutations of statistics; at least I thought we had run out all the possible statistics, until Dr. Ivy pointed out some deficiencies to me this morning. I didn't think that anybody read the statistics in that book (Carcinoma of the Stomach, by Walters, Gray, and Priestly, Saunders, 1935) except Dr. Ivy, who reads everything, until the other day when Dr. Barrett asked us to explain a paradoxical finding contained in them. Among other things we "ran," as we cardpunchers say, gastric acidity against this and that. We ran gastric acidity against resectability and found perfectly clearly and regularly that the resectability rate was lower the lower the gastric acidity, and the regression included achlorhydria; that is,

achlorhydria cases had the lowest percentage of resectability. We also ran gastric acidity for the resectable cases against hospital mortality, and here again the findings were clear and what you might call reasonable. That is, the hospital mortality was higher the lower the gastric acidity, and here again achlorhydria fell in line, i. e., the cases with achlorhydria had the highest hospital mortality rate following resection. We then ran gastric acidity against survival rate after resection, and here, too, so far as the cases were concerned, the findings were consistent, the cases with lower acidity having lower survival rates regularly than those with higher acid. But not for the cases with achlorhydria: these had a higher survival rate. So with all the damnation that has been heaped on low acids today by Dr. Rigler, Dr. Comfort, and others, I want to record that there is one peculiar piece of statistical evidence that some kinds of achlorhydria seem to be good at certain times. If you acquire a carcinoma of the stomach, can get your lesion resected, can survive the operation, and are achlorhydric, then you are better off.

Dr. Owen H. Wangensteen: I don't know whether comments from a clinician are in order at this juncture or not. With respect to Dr. Berkson's observation on survival in achlorhydric patients, I might suggest that the employment of closed anastomosis, which some surgeons employ for gastric resection, might be a very important determinant whether a patient will survive or not.

As Dr. Pack said this morning, surgeons are doing a much better job in getting patients to survive the operation than they did some years ago. I think he said that about 25 percent was the general mortality of operation a few years ago when he and Livingston wrote their book. Last year, in the surgical clinic of the University of Minnesota Hospitals, 58 patients underwent resections for gastric cancer, including 8 gastrectomies. The operations were performed by a number of surgeons. There were 2 hospital deaths in the series, a mortality of 3.4 percent.

Now, as Dr. Pack intimated, I think that as we get up into the thorax and do the combined thoraco-abdominal operation, we cannot sustain that low mortality. Last year, of all the patients with gastric cancer who came to the University Hospitals, we resected 85 percent. Obviously some of these were not curative operations but palliative resections; and of those that were operated upon, 90 percent were resected. Surgeons can deal with the difficult technical problems presented by patients with gastric cancer. We can resect the colon or the small intestine or take out half the pancreas if need be, in addition to the gastric resection. If, however, we are to make a better ultimate showing with the problem of gastric cancer, obviously we must get the patients earlier.

As a correlative of Dr. Pack's suggestion of more radical operation for gastric cancer, I would say that in gastric cancers that involve the transverse colon, or exhibit lymph-node involvement of the transverse mesocolon, wide excision of the colon and its mesentery, something akin to total colectomy, is in order. It is just as easy to take out a greater portion of the colon as to take out a small segment, and the more radical operation constitutes a far better operation for cancer.

As a surgeon, I think we have been working on the wrong side of the woodpile in the gastric-cancer problem. The cases are piling in at the other end. We want the fresh cases that Dr. Dailey spoke of today. The question is just how to find them. I am in sympathy with his suggestion, but I should not limit examination to patients who have symptoms, for a large number of patients with gastric cancer are asymptomatic; and if patients may have silent cancers, we have to examine the patients to find such silent malignancies.

You recall from Dr. State's presentation and from Dr. Ortmayer's that there was a real analogy there with reference to the incidence of polyps in the stomach and rectum. She had 2 percent rectal polyps in her cases; Dr. State had 3 percent gastric polyps in achlorhydric patients. Yet if every patient were gastroscoped, I suspect the incidence would be even greater. If the instrument Dr. Benedict showed us this morning could be swallowed voluntarily by more patients coming into our clinics, we should find more polyps.

You recall that Dr. State said, too, that in Dr. Wetherby's series published in 1940—and Drs. State and Varco have had the opportunity of following those patients of Dr. Wetherby—the incidence of gastric polyps was 6 percent. What the lag interval between the beginnings of a gastric cancer and the onset of symptoms is, is hard to say. Patients who have undergone gastric resections, in whom we believed we did a complete operation but in whom the pathologist finds evidence of residual gastric cancer in the proximal line of resection, ordinarily get on well and remain asymptomatic for 15 to 18 or 20 months before the cancer begins to reassert itself and to cause symptoms.

As Dr. Ortmayer said, it is difficult to know sometimes whether a rectal polyp is malignant or not. Moreover, we do not get too much help from the pathologists, either, in the solution of the problem. I agree with Dr. Ortmayer that we should try to define some definite histologic criteria of what constitutes malignancy in such polyps. The pathologist will gladly tell us it is cancer when the polyp exhibits evidences of invasion; but we should have some suggestion from the histologic appearances or characters of the polyp per se with-

out the added item of invasion to determine whether a given lesion is cancer.

For instance, with reference to the gastric-polyp question, the definition of such criteria would be very helpful in indicating what attitude the surgeon should assume toward the presence of gastric polyps. In patients who have a polyp, if no satisfactory scheme is yet available to take a biopsy, we could make an incision and get a fragment of the polyp out, have it examined, and some months or years later remove another fragment for examination.

I must confess that in our clinic we have become somewhat more conservative concerning the potential malignant character of gastric polyps. We thought at one time that they were all precancerous, and as Dr. State said, we resected the stomachs of a number of patients with gastric polyps. But after taking out a number of rather innocent-appearing polyps, one begins to wonder whether he is justified in doing it.

Many of you know that Spriggs and Marxer in England have reported patients with gastric polyps that have been observed over a long period. Dr. Broders, of the Mayo Clinic, has used the term "cancer in situ." I think that it is a very good expression. If some of these polyps are cancer in situ, we ought to find out whether that is true.

My associates and I feel that employment of achlorhydria as an approach to examination of silent carriers of gastric cancer is worth while. It will not catch all gastric cancers. If we could find something that would catch them all, of course, we should lessen the labor. In the Columbia study of Dr. St. John and his associates, 2,413 cases were examined, among which 3 cases of malignancy were found. In Dr. State's study there were 310 cases, among which 2 cases of gastric cancer were found, 10 polyps, and 2 or 3 additional cases of gastric cancer that should have been caught but were not caught because of organizational errors. The tragedy of it is that even some of these silent gastric cancers found were not early cancers.

Dr. Templeton: In patients having high gastric acidity, the carcinoma is, I think, usually ulcerated. It is the ulceration that brings the patient to the surgeon in the early stage of the disease, for it is known that small ulcerated lesions are more easily detected at X-ray examination than are the small infiltrating lesions. In most instances, the roentgenologic evidence is the major factor in determining whether the patient should be sent to surgery or not.

If a group of patients known to have very early carcinoma were presented to me for roentgenologic examination, I doubt if I could find many of the lesions. Therefore I should like to ask Dr. Strong if he can describe the appearance of the very early carcinomas which occur in his mice. Is there some gross evidence of their existence? Is the change all microscopic? If there is some gross evidence of their existence, we roentgenologists might have a reasonable chance of finding it with our present methods.

Dr. Strong: In living animals I usually palpate the stomach tumors before they are killed, and of course, knowing the age of the animal and knowing the genetic background, I can predict that if I kill certain animals they will show certain lesions. I don't need X-ray for this purpose.

Dr. Peacock: I should like to ask Dr. State and Dr. Comfort about bile in the gastric analyses they made. I don't think anyone mentioned bile regurgitating through the pylorus. I have a suspicion that perhaps that might have some importance in relation to achlorhydria, hyperchlorhydria, or in other words to the pH of the gastric juice.

My reason for saying that is this: There must be some reason why tumors of the stomach are more common near the pylorus than elsewhere, and we know that bile is a good solvent for the better known chemical carcinogens, and under the action of acid it can be neutralized, and precipitations can occur. I won't say more about that today, because I see you have put me down to say something tomorrow. But I should like to ask whether in the gastric analysis bile was found in the cancer-precursor group, or if there were cases in which it did not occur.

Dr. Comfort: I can't give a numerical answer to your questions, but certainly gastric contents not infrequently contain a small amount of bile.

Dr. State: I think my answer would be just about the same as Dr. Comfort's.

Dr. Hollander: May I ask a question of Dr. Ivy about the work he reported this morning? You developed a chronic ulcer, presumably by reason of the fact that rough food was constantly irritating the regions of excised tissue with which it came in contact. Now suppose, for the sake of argument, that you had succeeded in inducing a malignant transformation in some of the cells, is it not likely that those cells might be rubbed off by that very same roughage, and that for that reason you would have failed to develop any sort of tumor?

Chairman Ivy: Yes, I think that is possible. But the same thing should happen in the human case in which it is believed that cancer may arise in the margin of a peptic ulcer due to exogenous irritation. I believe this hypothesis should be carefully and faithfully tested. I believe we should go as far as requiring evidence of metastases before we can claim that cancer has been produced by means of such a method; i. e., we should obtain some gastric cancers with metastasis. My own opinion is that we should not call a tumor a cancer

until we have definite evidence that it has metastasized.

Dr. Fern Smith (Yale University): I should like to ask Dr. Rhoads if he has any microscopic evidence in the kidneys or the adrenals or the liver to add to his biochemical material he gave this morning.

Chairman Ivy: Is Dr. Rhoads here? I believe I observed him leave the room a few minutes ago.

Dr. Pack: I can answer that, Dr. Ivy, by saying that at the time the biopsies are made of the liver, which is done routinely for every laparotomy in which a patient has gastric cancer, a portion of a specimen of the liver is sent to the laboratory for histologic study, and there have been no findings under the microscope which would suggest any defect, at least in the anatomy of the liver, even though chemical changes have been quite marked. But no sections of the adrenal or of the kidney were taken at that time. We anticipate doing this.

Dr. Figge: Because of some remarks that followed my previous remarks (laughter), I am going to amplify what I said because I fear that I may have been misunderstood. Now, I did not intend to cast any aspersions on any of the papers that dealt with achlorhydria or the acid content of the stomach. What I am objecting to is a custom that is out of date, and I hope that if we meet again 5 years from now we shall be describing gastric acidity not only in volumetric terms but also in terms of pH. I still maintain that if it is a good thing to evaluate a factor in a semiquantitative way, it certainly can do no harm to evaluate it more quantitatively.

Dr. Daniel Laszlo (Montefiore Hospital, New York): I should like to raise two questions: (1) Assuming that it is proven that the hydrochloric acid production in the stomach is depressed significantly in patients suffering from gastric cancer, is there a causal relationship between both? (2) Dr. Benedict stated his impression that patients suffering from pernicious anemia develop both gastric and extragastric malignancies at a higher rate than do nonpernicious-anemia patients. Would this indicate, if confirmed, that these patients, who lack the hematopoietic principle, lack some unknown antimalignancy factor as well?

Chairman Ivy: Dr. Rigler, will you answer the questions?

Dr. Rigler: Is Dr. Benedict here?

Chairman Ivy: Here is Dr. Benedict. Pardon me.

Dr. Benedict: I haven't any answer. I put that idea up as a remote possibility. I didn't say this is a fact. I though that this is a cancer conference, and we are interested in grasping at straws. I do think, however, that tumors of the stomach are more common in gastric atrophy than in normal gastric mucosa.

Dr. Rigler: I just wanted to add our impressions, since Dr. Comfort's data (he certainly comforted me a great deal, incidentally) seemed to indicate clearly that in a certain type of gastric cancer the achlorhydria precedes the development of the cancer. That is, of course, what we think is the case in pernicious anemia. Pernicious anemia being a disease which produces symptoms and is recognized readily, it is conceivable that we are recognizing the pernicious anemia and not recognizing the cancer which may already be present in some microscopic form and which is giving no manifestations that we can detect. That is conceivable, but the evidence seems to point in the other direction, so that we think the achlorhydria precedes both.

I might say that in the autopsy studies that Dr. Kaplan and I did, we ran down one group of tumors other than carcinoma of the stomach to determine the relationship to pernicious anemia, but we found no particular coincidence. We ran only one tumor group as a sort of control.

I also want to add something about the question of early diagnosis. No one, of course, would disagree with Dr. Palmer that every patient with dyspepsia should have an X-ray examination of the stomach. That would be ideal and probably won't be achieved in our generation, but I think one should look at the figures from the Mayo Clinic where I am sure everybody with dyspepsia has X-ray examination of the stomach, or from our clinic, and see how many early cancers were discovered by that method. I am sure that from our experience both with the achlorhydric group and with the pernicious-anemia group, we have to find cancer of the stomach before it produces dyspepsia if we are going to make any real impact on the problem.

In regard to Dr. Templeton's pessimism on the problem of finding the lesion, I think that it is not entirely justified. Our own experience, in spite of a number of errors which we regret, has indicated that you can determine the presence of very small carcinomas. As a matter of fact, my experience is quite different from his. We think we find the polypoid type of carcinoma very easily, and in that respect, therefore, achlorhydria, which is almost always present in the polypoid type of carcinoma, would perhaps be diagnosed earlier than would the infiltrating or ulcerative type. Certainly in that group very small lesions can be determined by X-ray examination. I think that my own impression is clearly and very emphatically that fluoroscopic examination alone will not result in the detection of these lesions; films have to be made, and care has to be taken in the examination of the films. I have the impression, in fact, that if we had to choose between making a film examination of the stomach

and a fluoroscopic examination for the detection of small lesions, I should prefer the film examination to do it. Obviously, the two methods combined are by far the best.

Dr. Laszlo: I have evidence to believe that suppression of the HCl formation in the stomach is accompanied by suppression of a number of other lesser known partial functions of the gastric mucosa, some of which are of probably greater significance for the development of gastric cancers than is the hydrochloric acid secretion itself.

Dr. Ross Golden (Presbyterian Hospital, New York City): Our ability to detect cancer of the stomach by X-ray methods depends upon two factors: (1) The position of the growth in the stomach; and (2) the gross growth characteristics of the lesion.

I went over 205 cases of proved carcinoma of the stomach and found that 75 percent of them apparently originated in the antrum below the incisura angularis; 20 percent of them originated between the incisura angularis and the level of the cardiac orifice; and only 5 percent of them were in the fundus above the level of the cardiac orifice. So we have at least 3 chances to 1 in our favor, as far as this first factor is concerned, as it is much easier to detect a growth in the lower than in the upper half of the stomach.

I am greatly indebted personally to Dr. Arthur Purdy Stout for his conception of the classification of carcinomas of the stomach. The microscopic character of the cells is of no importance in this problem. The gross growth characteristics, however, are of profound importance, as implied by Dr. Rigler and Dr. Templeton. Dr. Stout divides these cancers into 4 groups: (1) The fungating type which grows into the lumen and produces a mass. In the last 200 cases this group comprised only about 25 percent. (2) The spreading carcinomas which extend along the wall and which he divides into 2 subgroups: (a) The superficial spreading, which grows along the mucous membrane and often, but not always, into the submucosa but not into the muscle. This comprised 14 percent of 200 cases; and (b) the linitis plastica type in which the growth extends through all coats of the stomach and which comprised 2.5 percent of 200 cases. (3) Penetrating carcinoma which begins in the mucous membrane and quickly goes straight through to the serosa. These cancers invariably ulcerate. They comprised 25 percent. (4) Cancers which have developed so far that a classification from the standpoint of gross growth characteristics cannot be made. They comprised 32.5 percent of the 200 cases.

The superficial spreading carcinoma was first noted by Dr. Stout in the Department of Surgical Pathology at the Presbyterian Hospital in 1937. Since then, he has collected 28 cases, of which over 80 percent were ulcerated. Inasmuch as the superficial spreading and the penetrating cancers do not produce masses, the ulceration adds greatly to the ease of detection. Of the 28 cases, 7 developed around the margin of an existing open peptic ulcer, and 8 developed in the mucous membrane covering the scar of a healed peptic ulcer.

Dr Irving Ariel (VA Hospital, Hines, Ill.): Concerning gastric acidity, 4 years ago in reviewing about 100 cases of gastric cancer in conjunction with Dr. Pack and studying various abnormalities, we found that a great many patients with gastric cancer had normal gastric acidity, and a few even had hyperacidity. As a result, utilizing gastric acidity as a diagnostic procedure had very grave limitations. Therefore, I should like to ask Dr. Comfort if he has studied patients with achlorhydria exclusive of those with carcinoma over a long period. Also, is anyone here willing to explain the presence of a great deal of acid, including hyperacidity, in patients with gastric cancer? The theme here seems to be to explain the gastric cancer developing upon a stomach that does not produce acid.

Dr. Comfort: We have not completed a follow-up study of an unselected series of cases with gastric anacidity but plan to do so.

Dr. Pack: I should like to say a word of defense of New York City, if I may, because of the remarks that Dr. Rigler and Dr. Wangensteen have made. These pessimistic figures that I presented were about 8 years old, and they have been improved upon. As I said, in a gastric service at the Memorial Hospital, the resectability has increased so that at the present time it is 40 percent of those patients applying to the hospital. It is not 40 percent of those finding their way to gastric service, but 40 percent of those who crawl through the doors of the hospital, however they are brought.

Of course in New York City with the number of people to draw from and the proximity of Memorial Hospital to the East Side, and all these other districts, any patient with gastric cancer, who can be brought there no matter how sick he is, once entering the doors of the hospital and being registered, is included in this figure. We shall never be able to approach the figures of the Mayo Clinic, Dr. Berkson, as you know, because after all you draw from the entire world, and people have to be well enough to get to Rochester.

Regarding Dr. Wangensteen's figures, I visited his clinic several times; and of course every time I hear him speak and see his work, I am stimulated by his great courage and by his extraordinary ability. But no matter how heroic or how herculean our efforts in trying to resect gastric cancers, I don't believe we shall ever approach a figure of 90 percent, such as you have done, in patients sub-

jected to laparotomy. I wonder how you can limit exclusion to as low a figure as 10 percent.

Nor do I believe we shall ever be able to approach a resectability of 85 percent of the patients admitted to the hospital; and I am quite sure that at no place in the world today is there any other clinic that can present as good figures. I believe your figures are accurate as they come to you, but isn't there some way in which those patients are screened before they come to your service? Does that represent the percentage of patients with gastric cancer as they come from their homes, or from off the street, to apply to the admitting office for diagnostic service in your hospital? If that is true, I think you have reached the very peak of proficiency in early diagnosis, and I congratulate you. I believe you are as nearly correct as is possible. I agree to that.

Figures from St. John's work were presented today, that in a survey of some 2,500 consecutive persons who did not have symptoms referable to the stomach, 3 or so were found who did have gastric cancer. That doesn't seem to me to offer much promise to extend the scope of surgery. There are many surgical clinics in the United States today in which the surgeons are content to do gastrectomy, but they are denied the opportunity. If we take a comparable group of 2,500 patients with gastric cancer, and a number of patients of those in whom total gastrectomy or transthoracic gastrectomy can be done, it will mean that 150 patients will have an opportunity to be cured by extending the scope of surgery, as compared with 3 patients in whom we try to establish X-ray diagnosis in the absence of symptoms. Both should be done.

Dr. Wangensteen: May I ask Dr. State, who is familiar with details of the cases that come to the hospital, to answer Dr. Pack?

Dr. State: The figure of resectability was based upon the number of patients who were seen in the out-patient clinic and in whom a diagnosis of carcinoma of the stomach was made; that figure includes patients who were not only admitted but also had a diagnosis of carcinoma of the stomach made in the out-patient clinic.

Dr. Berkson: I want to say that in the early part of this meeting I was somewhat distressed by the fact that there was considerable dispute about genetics. I want it clearly understood that it is statistics that has the prerogative of being the disputatious subject! Now that everyone is beginning to cast doubt on everyone else's statistics I feel at home again. Dr. Pack has said a word on behalf of New York City. I should like to say something on its behalf too. Statistics are collected erroneously and are interpreted falsely. But when we say this, we are not talking about Dr. Pack's statistics. Dr. Pack's data are compiled with extraordinary care and are extraordinarily critically analyzed, much as it pains me to have to ackowledge this for a mere surgeon. But whether the data are from Rochester (Minn.) or New York City, they merely furnish a base line for investigation. As Dr. Pack has said, we are dealing in clinical material with selected populations, and quick generalizations regarding the general cancer population cannot be drawn. I do not mean that clinic statistics are valueless, far from it. While I am on my feet, I should like to put in a plug for the expenditure of some of the available funds to set up standard procedures for and the acquisition of properly calculated survival rates of cancer patients in the large cancer clinics of the country. If we could get definitive hospital mortality and survivorship figures for the whole country, it would be a capital contribution to the cancer-study program. It really would not be hard to do if set up properly. If you wish to know how to do it, you don't have to come to Rochester, you can go to Dr. Pack in New York City.

Dr. Wangensteen: I should like to say one other thing, and I should like to use the blackboard. Dr. Pack stated that he and Livingston had found in their survey of the world's literature that 98 percent of patients reporting to hospitals with gastric cancer died within 5 years. That is a very discouraging prospect. Yet in the Mayo clinic figures, the best reported in the United States to date, Dr. Berkson (1942) stated that 94 percent of patients coming to the Mayo Clinic for gastric cancer had died of their cancer within 5 years. The best figure for ultimate recovery, known to me, in the world's literature is the report by Weese (1940) from the Tuebingen Surgical Clinic. After 5 years, 92 percent of patients coming because of gastric cancer were dead. Whereas there appears to be a 400-percent difference between 2- and 8-percent survivals, the actual disparity is more real as suggested in the smaller difference between 92- and 98-percent mortality.

Dr. Pack and his associate, Dr. Livingston, deserve the greatest commendation in giving us an excellent prototype for the best kind of factual monograph, which proves helpful in analyzing the accomplishment in this field. This book deserves the compliment of imitation, the sincerest kind of praise. Those of you who are unfamiliar with Livingston and Pack's book, Carcinoma of the Stomach, would do well to read it.

Dr. Hollander: May I ask, Dr. Berkson, whether the difference between 2, 6, and 8 percent simply arises from the sampling error?

Dr. Berkson: It is a very small quantity.

Chairman Ivy: There is one point that I should like to direct to the attention of those who have been interested in the question of the relation of

pernicious anemia to gastric cancer. As I am familiar with that literature, there is a higher degree of correlation between the concomitant occurrence of pernicious anemia and gastric carcinoma than that of any other disease with gastric carcinoma. There is evidence that there is a hereditary trend in pernicious anemia. We frequently assume that such is the case in gastric cancer. We know that the iso-agglutinins of the blood groups are inherited; we know that the iso-agglutinins of the blood groups are concentrated in the gastric mucus and that they probably come from the "neck" cells. The neck cells are the cells that are most likely concerned in the formation of gastric carcinoma. Hence, it would be of interest for those who are interested in this question to study the blood groups of their patients in relation to the presence or absence of cancer. (Pause.) Is there any other discussion? If not, we stand adjourned.

The meeting recessed at 5 o'clock.

FRIDAY MORNING SESSION

DECEMBER 6, 1946

The meeting convened at 9:30 a. m., Dr. R. R. Spencer, Chief, National Cancer Institute, presiding.

Chairman Spencer: The conference will please come to order. The first item on the program this morning is a discussion of a comprehensive outline of attack on gastric cancer by Dr. Andrew C. Ivy, vice president of the University of Illinois. Dr. Ivy.

Dr. Ivy: The Committee on Gastric Cancer, of the National Advisory Cancer Council, met this fall to consider the question of an over-all attack on the problem of gastric cancer. It was felt that this is important because so many people die of gastric cancer, and at the present time there seems to be a great deal of negativism relative to the possibility of success in decreasing the death rate from cancer of the stomach. There also seems to be a question regarding the advisability of carrying on a detection program for cancer of the stomach. And relatively little research is being specifically directed to the subject of gastric cancer.

I believe that a discussion of the general aspects of a large problem by a large number of individuals is very much worth while. As a general rule, when a scientist is confronted with a problem, he first attempts to analyze it in order to find out the most advisable experimental approaches. I believe that such a procedure is applicable to the gastric-cancer problem.

Drs. Barrett and Helen Dyer, of the National Cancer Institute, were asked by the committee on cancer to review the literature, to study the problem, and to analyze it insofar as the various avenues of attack are concerned. This effort will be published by Dr. Barrett later [Jour. Nat. Cancer Inst. 7: 127–157, 1947]. What I wish to do is to present various aspects of the attack on the problem for your consideration and discussion. There is need to know more about the chemistry or metabolism of the cells of the gastric mucosa; this requires little emphasis among biologists.

One of the first needs, I believe, is a registry for gastric cancer or for cancer of all types. The State of Connecticut has gone a long way in developing a registry. This need for an over-all attack on gastric cancer should be emphasized. The need was pointed out at the Conference on Gastric Cancer in 1940, and I believe that it deserves reiteration and emphasis at this time with the hope that either the Federal Government or the various State governments—I believe the latter would be best—will establish or assist in the establishment of such a registry in each State.

Second is the question of education: First, education of the profession. I believe that the most important point that should be impressed on the profession is the fact that gastric cancer is no longer a hopeless condition. The marked improvement that has occurred in attaining 5- and 10-year cures, I believe, demonstrates without any question of doubt that gastric cancer does not present a hopeless condition. We should get that idea across to the general profession, because, according to pathologists, 20 percent of the persons that die with gastric cancer have a lesion which is confined to the stomach and adjacent lymph glands.

In regard to nonprofessional education in relation to gastric cancer, the question arises, What should we tell the public? Should we tell people that they should only come in for detection of possible cancer of the stomach after they have the symptoms of dyspepsia? Or should we tell them to come in for X-ray examination before they develop the symptoms of dyspepsia, and, if so, how frequently should we tell them to come? Is a gastric-cancer-detection program worth the cost? Those are very practical questions, and we should have some generally established answer to them before we can, with any degree of assurance on our part, educate the public.

A third problem pertains to the heredity of gastric cancer. The number one solution, in my opinion, is to improve the collection of data on the question by setting up cancer registries in our States.

Yesterday I mentioned a second point in relation to the heredity of gastric cancer which is worthy of investigation at this time. Is the occurrence of cancer of the stomach in any way related to blood groups or Rh negativeness? This

question is based on several facts, namely, that agglutinogen A and B in the red blood cells is concentrated in gastric mucus, that heredity is concerned in the determination of blood groups, that it is possible that premature achlorhydria and pernicious anemia are hereditary, that the predisposition to cancer of the stomach is hereditary, and that the patient with pernicious anemia seems to be predisposed to gastric cancer.

A fourth problem is the relation of hormones to the problem of gastric cancer. When this subject is mentioned, the difference in the sex incidence of cancer of the stomach comes to mind. The autopsy statistics from the Bureau of the Census and also from the Metropolitan Life Insurance Co. show that cancer of the stomach occurs in 2.2 percent of the males, and 1.5 percent of the females. In other words, there appears to be a definite tendency for cancer of the stomach to be more frequent in males. And that is true of all age groups, or all decades in which cancer of the stomach occurs. On the other hand, carcinoma of the gall bladder and liver has a higher incidence in the female. That is related, perhaps, to the higher incidence of cholecystopathy and gall stones in the female. We should have available and should try to obtain information that explains this difference. The question is related to premature anacidity, which is more frequent in females.

As regards the hormones which are specifically concerned with gastric activities, there are a number of problems worthy of investigation in that field, but I do not believe they deserve emphasis on this occasion.

The fifth problem pertains to the relation of atrophic gastritis to gastric cancer. From an experimental point of view, it is believed that further attempts should be made to produce atrophic gastritis. Dr. Hollander's work should contribute much to this problem. In addition, Dr. Lushbaugh presented to us yesterday morning his observations on monkeys, in which the feeding of a shale oil apparently caused the production of hypertrophic gastritis, which, in one instance, as I recall now, was followed by atrophic gastritis. In this connection, I believe it would be definitely worth while to consider the advisability of breeding monkeys or rats in this direction. If an atrophic gastritis can be produced in one animal, an attempt to breed in a susceptibility to atrophic gastritis should be undertaken. In the clinic, it is my opinion that patients with chronic atrophic gastritis, diffuse or patchy, should be followed, and that facilities should be rendered available for following such cases and correlating the microscopic and gastroscopic findings.

A sixth problem pertains to the concomitance of gastric cancer, and I believe that the study of this problem should be continued along with heredity studies.

A seventh problem pertains to the relation of premature achlorhydria to gastric cancer. If the larger clinics cannot provide the answer to this problem, recourse to a registry will be necessary, provided it becomes that important.

The eighth item on my list is a study of gastric polyps. A study of this type was presented to us yesterday from the clinic at the University of Minnesota. Since polyps do occur in dogs and perhaps other laboratory animals, one might consider the advisability of the inbreeding of a strain of animals with gastric polyps, with the idea that the polyps might undergo carcinomatous degeneration, as is generally considered to be true in the case of the human colon.

The ninth question pertains to the relation of gastric ulcer to gastric cancer. There is plenty of room here for an experimental study. It is possible to make acute ulcers in the glandular stomach of the rat and to feed carcinogens. Unfortunately, acute ulcers made in the glandular stomach of the rat heal rapidly, within 5, 10, or 12 days, even when they are rather large. This means that the carcinogen would have only a brief time to act on the proliferating fibroblasts and neck cells in the base and margins of the ulcer. The rabbit and dog are very resistant to carcinogens, but a chronic gastric ulcer can be produced in them. If we had a very potent carcinogen, we might cause a cancer to form in a gastric ulcer.

From the clinical aspect of this problem, I believe more emphasis should be placed on the possibility that a gastric ulcer may be a malignant ulcer. The rate of healing under strict medical management with frequent X-ray examination should be studied more carefully than in the past. We should try to find some way to improve the present diagnostic methods for differentiating between a benign and a malignant gastric ulcer. At the present time, when one considers that question, a solution looks hopeless; but we should not approach the problem in that spirit, because, if we do, we shall never solve it.

The tenth problem I have on my list is the relation of duodenal ulcer to carcinoma of the stomach. The clinical literature claims that it is very rare for a patient with a history of duodenal ulcer to develop a gastric cancer. I have looked carefully to find some data supporting that clinical impression and have been unable to find any. I believe that we should collect some data on the subject to ascertain whether it is a fact. If, for example, as some maintain, achlorhydria or premature achlorhydria is the sign of a precursor group and occurs in about 10 percent of our population, and cancer tends to occur in that group; and if, on the other hand, hyperchlorhydria and

duodenal ulcer are found in 10 percent of the population, and hyperchlorhydria represents a precursor group for duodenal ulcer but not cancer, then, if that is true, we shall have an important biologic phenomenon of etiologic significance.

An eleventh suggestion is to consider the advisability of making surveys to find areas of high incidence. If we could find certain areas in which the incidence of carcinoma of the stomach is strikingly high, we could study the people in those areas to attempt to find the causes.

A twelfth item pertains to the relation of diet to cancer of the stomach. As you know, considerable has been written on this subject. As regards the relation of diet to gastric cancer, there are no convincing results in the literature. Dietary irritants are frequently mentioned as a possible cause. The only experimental evidence on this subject with which I am familiar is that provided by Dr. Roffo, of Buenos Aires. He reported that if he fed his particular strain of rats cooked fat or heated fat that had been exposed to ultraviolet light, they would develop cancer of the stomach. The evidence he published is not so convincing as one would like, but on the other hand it is possible that Dr. Roffo has a strain of rats that may be susceptible to some agent produced by heating fat. On the latter hypothesis I have been able through Dr. Roffo and Dr. Tanturi to obtain some of the Roffo strain of rats, and we shall treat the rats as directed by Dr. Roffo.

The thirteenth problem on my list is to find a consistent method for the production of cancer of the stomach. At the present time it appears that cancer of the stomach has been produced experimentally in two different ways: (1) By injection of carcinogenic hydrocarbons into the gastric mucosa of the rat; and (2) by the breeding experiments of Dr. Strong. The first method is not sufficiently consistent to serve as a worthy experimental tool, and the latter does not yield a sufficiently stable tool to use at present. When a satisfactory method is available for consistently producing gastric cancer in the rat, we shall then be able to assay substances for their inhibitory value. This would greatly facilitate the study of gastric cancer.

Item fourteen on my list is the question, Is it possible that gastric cancer may be caused by the action of bile on the gastric mucosa? This question arises because a number of the carcinogens are chemically related to cholic acid, and because bile affects the viscosity of gastric mucus and the permeability of the pyloric mucosa to various dyes. For example, bilirubin does not stain the pyloric mucosa except when in solution in bile. When bile is drained into the stomach of man and animals, gastric cancer does not occur. However, no long-term observations on this point have been made.

I have left to the last the question whether it is worth while to undertake a detection program for cancer of the stomach. At present, in most detection clinics, detection is directed principally to the superficial cancers, cancer of the vagina, the cervix, the breast, the skin, the lip, and the mouth. The stomach is usually not examined unless the patient has symptoms of dyspepsia.

I have placed some data on the blackboard to indicate what might be accomplished by an extensive program for the detection of gastric cancer. About one-third of our population today is above 40 years of age, which means that there are in our country today approximately 47 million people above 40 years of age. Ninety percent of the cases of cancer of the stomach are in persons above 40. Patients with a carcinoma of the stomach live on the average about 1 year after onset of the symptoms. Since 40,000 die every year, there must be approximately 80,000 cases of cancer of the stomach in our country at present.

If we divide 80,000 into 47,000,000, and if we make a survey on the basis of this incidence of cancer of the stomach, we shall find 1 cancer in every 588 persons over 40. If we use the figure 40,000, then we shall find 1 cancer in every 1,175 persons over 40.

St. John, Swenson, and Harvey found 3 malignancies in examining approximately 2,400 persons. They found 1 cancer in every 800 persons above the age of 50. On this basis the probable range of these considerations lies somewhere between 1 in 600 and 1 in 1,000 in persons above 40 years of age.

If you take some data supplied by Drs. Pack and Livingston and by Drs. Walter, and Gray, and Berkson, and by pathologists, 20 percent of the people who die of cancer of the stomach die with the cancer confined to the stomach or adjacent nodes. And in the hands of some surgeons, 20 percent of the unselected resectable cases yield 5- to 10-year cures.

Now if we take one-fourth of 40,000, we have 10,000 new resectable cases developing each year. If we can obtain 20 percent 5- to 10-year cures by our present methods, the methods that have been employed during the last 10 or 12 years, then out of this group of 10,000 new cases we shall obtain 2,000 5- to 10-year cures. There is reason to believe that that 20 percent can be raised to 25 percent, and some would urge up to at least 30 percent. If by conducting a general detection program we could get these cases earlier so as to increase the percentage in the 20-percent group, in which the cancer is still confined to the stomach or regional lymph glands, by 100 percent, then we should increase the 5-year survivals to 4,000 or 5,000, or we should be able to get 5- to 10-year cures in one-half of the new cases that are now developing.

As I have studied this problem, I believe that it is definitely worth while to perform studies which will give us evidence on this question of whether or not we should carry out on a large scale a detection program for cancer of the stomach.

Here is a question for which I have been unable to find an answer: In what percentage of the gastric-cancer cases that are resectable or not resectable does the cancer show up on an anterior-posterior film? Obviously, all those patients that would presumably come in to be examined for cancer of the stomach could not be fluoroscoped, but an anterior-posterior film could be made. How many more would we add to this list if we made a lateral and an oblique film, or if we made an anterior-posterior film and two oblique films? In other words, if we are going to have a large group of people report for films of their stomachs, should we make just one film, anterior-posterior, or should we make two or three films?

This is still another question: Should we be satisfied with the methods that we have at present? Should we not study serologic methods? Should we not direct attention in research to some rapid method for detecting cancer of the stomach similar to that which has been developed for detecting TB of the lungs, by the use of the 16-mm. film, or some other improvement of X-ray technique? In this connection, we must remember that some radiologists were against the so-called rapid method of detecting TB of the lungs, and we must keep in mind the fact that there is going to be some objection to using any rapid method to detect cancer of the stomach. The historically literate person will not take "no" for an answer. There are going to be some errors, as indicated yesterday, and as indicated in all the literature on this subject. Even with the most experienced roentgenologist using the best method, there is an error inherent in the diagnosis of cancer of the stomach, either early or late. Some figures show that the accuracy is only 75 percent. I was discussing this matter with someone yesterday, Dr. Pack I believe, who said that their accuracy is around 92 percent. That includes all sorts of gastric cancers and not only early cancers. Of course I think that it should be made clear that no detection program for anything can guarantee 100-percent accuracy.

I should like to know the consensus of this group regarding whether it is worth while to encourage studies to discover a method for improving the detection or the finding of gastric cancer.

I thank you.

Chairman Spencer: I am sure everyone here is grateful to Dr. Ivy for this very comprehensive outline of a possible attack on the cancer problem. The discussion will be led by Dr. P. R. Peacock, of the Glasgow Royal Cancer Hospital. Dr. Peacock.

Dr. Peacock: Dr. Spencer, Ladies, and Gentlemen: This discussion, so far as I am concerned, is concerned with the experimental side much more than the clinical, because I am an experimental pathologist. The figures we listened to in yesterday's session presented, I think, rather a gloomy picture of the prospects of survival of a patient with even symptomless, early detected, gastric cancer. Although Dr. Ivy this morning has brightened the picture somewhat by presenting the probabilities or possibilities of improving the survival rate up to, say, 50 percent, even so under the very best conditions we are left with a picture which is very far from satisfactory.

Cancer of the stomach is the principal danger from cancer to the residents of the Temperate Zones of the world.

I think that we ought to consider that man is an experimental animal in a big way. He has an extraordinary tendency to experiment on himself, which is not shared by other animals. He has a tendency to develop habits which are far removed from what one can call natural habits. Statistics have to be considered to some extent as a replacement for deliberate experiment on man.

As a background for what I want to say, I should like to project quickly a few slides, some of which I am afraid cover somewhat the ground that Dr. Ivy has already covered. Could I have the first few slides in rapid succession? (Slides.)

These were taken from figures of Cramer, which he published a long time ago, relating cancer of the stomach and bowel in Holland with the same two diseases in England and Wales. Cancer of the stomach in Holland represents about half the cancer mortality, and in England and Wales about a quarter. There doesn't seem to me to be any strong reason for supposing that the genetic constitution of the Dutch people is so very different from that of the British, that such a difference could be accounted for in terms of genetics or hereditary predisposition.

In England Stevenson in 1921 analyzed the Registrar General's returns for cancer (slide) according to certain sites which he called exposed sites and others which he considered closed sites. The exposed sites included the upper respiratory tract and the upper alimentary canal, and there is a histogram in the upper and lower parts of this chart which is subdivided according to economic groups. He considered the population in five economic groups, the first being the best off and the fifth being the worst off. There seems to be no special reason why the people in the lowest economic group should have a hereditary disposition not shared by the people in the group best off, and it looks from this kind of observation as though

there were a real increased risk on the part of people in the lowest economic group in relation to cancer of the upper alimentary canal, which accounts for that high figure in the total exposed sites. That risk is not being shared by the people in the first two economic groups. These people are avoiding something which is causing cancer of the stomach in the group worst off economically. There is, therefore, I think, prima facie evidence for a part played by extrinsic factors over and above any part that may be played, and undoubtedly, as was shown yesterday, is played by such inherent tendencies as pernicious anemia and abnormal functional activities of the stomach in this disease.

This figure (slide) is really a small repetition of what Dr. Ivy has just shown, taken again from Cramer, in 1936 showing the relative distribution of the population below and over 65 years of age and the cancer mortality in the two groups. You can see that over 65 we have about a tenth of our population, as apparently you have, and yet there is about the same incidence of cancer in the over-65 as in the under-65 group.

That points, I think, to a thing we would expect if we were dealing with extrinsic factors causing cancer, and that is a long latent period. From what we know about chemical carcinogenesis in animals, we believe that a long latent period representing perhaps a third of the life of the animal is likely to be taken up by a period during which the particular tissue is exposed to the risk, and only after that long latent period is the result visible in what we call cancer. Statistical evidence, I think, also points to the probable presence of extrinsic factors conducive to human cancer.

It is extraordinary that cancer of the stomach is so common in man and so rare in animals. You may say at once that animals rarely have an opportunity to live out their lives to the full extent that human beings do, but in this part of the world the top lot of figures (slide) should be fairly well known. Slye's collection of mice, which were allowed to live out their lives, showed only a very small proportion that had developed cancer of the stomach. I think Dr. McPeak raised the figure, but I think she included only something like 10 or 15 cancers of the stomach in some 140,000 mice allowed to live out their lives, and I think 3 of these were adenocarcinomas.

I collected some few figures from South Africa. A special number of the Onderstepoort Journal was devoted to tumors in animals kept in zoological gardens where presumably they were allowed to live rather civilized and protected lives; there was only 1 adenocarcinoma of the stomach in the whole series, and that was in a horse—1 out of 119—and the bovines, ovines, goats, cavies, and birds had none. There was just 1 gastric adenocarcinoma in post mortems on 30 dags that died with tumors in Ruddick and Willis's series.

No doubt these figures could be elaborated, but they are enough to show that there seems to be reason to think that cancer of the stomach is not at all a common risk in animals, whereas cancer of other sites is quite common.

I think that one must seriously consider how extrinsic carcinogens may reach and act upon the human stomach. These figures, collected by Stewart, of Leeds, from post-mortem examinations of 263 ulcer cases, 17 ulcer cancers, and 84 primary cancers, show pretty clearly that there was a different site distribution in cancer and in ulcer, which I think is in agreement with generally supported views, and I have tried to illustrate that in a line drawing (slide). This is supposed to be a line drawing of the stomach, and the pyloric antrum is here, the danger area as far as cancer is concerned, whereas the ulcer area is higher up along the lesser curvature, and of course there is some overlap. But this pyloric-antrum area seems to be the site of most interest from the point of view of human gastric cancer.

Taking this area in a little more detail (slide), I have indulged in a little fancy here, by suggesting how extrinsic factors might come to act on this mucosa. The most obvious route is in food or drink, swallowed material of some kind, and the pyloric end of the stomach of course is in contact with food for a longer period than is the rest of the stomach. That has to borne in mind. But I think that it is also worth considering the question of a retrograde action of possible substances excreted in the bile, regurgitating through the pylorus and so meeting the mucosa just inside the pylorus and in the pyloric antrum. Physical factors might tend to concentrate any such effect in that pyloric region.

Now is there any justification for postulating such retrograde attack by carcinogens? I think there is a certain amount of reason to look for such an effect, although I don't think there is any positive evidence for the existence of such carcinogens at present, unless it be the demonstration, first by Schabad in Russia, and confirmed by Des Ligneris and by Hieger in South Africa and England, respectively, and later work by Steiner and others, that the liver of human beings sometimes, perhaps fairly often, contains a substance which can be shown to be carcinogenic by a subcutaneous-test injection into mice.

You may say that a subcutaneous injection into mice is a very different procedure and involves different factors from a direct action on the stomach. But from what we know of carcinogens, it isn't a very remote possibility. We know from the work of the London Hospital group that many chemical substances of the hydrocarbon type cause

cancer when painted on the surface, sarcoma when injected subcutaneously; and one of these same substances, methylcholanthrene, can cause adenocarcinoma of the stomach when it is injected into the wall in such a way that it is in contact with the mucosa, as shown by Stewart and Lorenz. So that when we have a train of evidence showing that carcinogens can be carcinogenic for many different tissues, a subcutaneous inoculation test may be of some value, as in detecting carcinogenic liver extracts. I have not succeeded in demonstrating any carcinogens in some 50 samples of human bile collected post mortem, but I do not think that such a test can be regarded as in any way conclusive. There is also the point that bile is an excellent solvent for some of the known carcinogens and that when we inject such hydrocarbons deliberately into the blood stream of animals, they are sometimes excreted in the bile, not only as the parent hydrocarbon but also in the form of hydroxy compounds.

Now if such substances should reach the human being's stomach, they might reach the pyloric antrum by both routes, directly through the food and subsequently after absorption and excretion in the bile by retrograde action. I only suggest that, because, after all, the purpose of this conference is to look into the future as well as into the past, and that might be a mechanism of some interest in the investigation of factors predisposing to cancer in the pyloric part of the stomach.

We ought also, I think, to consider that cancer is a cellular disease. It is most noticeable as a disease of a man or a woman, but it is a disease of the cells primarily, and it begins as a local disease predisposed to, no doubt, by bigger factors, such as pernicious anemia in this case. But it is a matter of some interest that even in the person who does develop cancer of the stomach only a few of these gastric cells undergo the malignant change. The great majority of them do not, although presumably they are exposed to the same risk.

Looking into the possible food factors, we repeated some of Roffo's work, and that work, coupled with the earlier work of Kennaway on the pyrolysis of organic substances, seems to give some prima facie case for thinking that heated foodstuffs, organic material of any kind heated to 350° or thereabouts might yield carcinogens. A temperature of 350° C. is about the temperature at which known hydrocarbons can be sublimed.

We tried, therefore, with common sources of fat, cottonseed oil, for example, to see if we could demonstrate any carcinogens. Dr. Beck has done a great deal of this work, and he showed by subcutaneous injections into mice that cottonseed oil heated to 350° for 1 hour yielded a carcinogen that would cause sarcoma upon subcutaneous injection of mice. Extracts of the same substance when painted on the skin induced a papilloma. Cholesterol, which also has been incriminated, was heated under similar conditions and again yielded a substance that would cause sarcoma in the subcutaneous tissues. The number of animals was small, but it has formed only a part of a program of a great many injections of a great many other substances, which were all negative, and I think that they should be regarded as positive evidence.

We then turned to feeding experiments and fed mice and rats emulsions in the drinking water suspended by means of the addition of soap solution, the suspensions containing 1 percent of cottonseed oil heated to 350° C. The rats and mice maintained on this diet, which was in other respects normal and adequate, for as long as they would live, yielded some results of interest. There were three groups. The first received heated cottonseed oil alone; the second received heated cotton seed oil plus 0.1 percent croton oil, which has been shown to have a procarcinogenic effect; and a third group received croton oil alone added to the diet.

Unfortunately, not many survived for long periods; but in the first group that received heated fat alone, an animal died at the six hundred thirty-first day with a palpable mass in the upper abdomen which I optimistically thought might be a tumor of the stomach and which proved to be a tumor of the liver, but it had a branching papilloma in the forestomach of the type that we get when we feed the known carcinogenic methylcholanthrene.

In the second group two of six survivors had tumors of the stomach. The first died with what I think was an undoubted carcinoma of the stomach, which I should like to show you (slide). I had forgotten this slide. This is just an example of some of the things that human beings do to their stomachs, and that animals don't do ordinarily. I think that all these things ought to be considered seriously.

This is not a very good colored picture (slide). This is a cross section of the stomach of a mouse. There is a large, obvious, tumor mass, involving a greater part of the circumference of the stomach and penetrating the wall.

This is the glandular portion of the stomach (slide), and these are normal glands; and here is, I think, undoubtedly an epidermoid carcinoma. This part up here is a mass of malignant tumor whose classification presented considerable difficulty. I interpreted it as an epidermoid carcinoma that had undergone central degeneration; and yesterday afternoon when Dr. Warren looked at the sections, he agreed with that diagnosis. The question that arises is whether this tumor arose only in the forestomach, the site where tumors are commonly induced with carcinogens in mice, or whether it also arose in the glandular part.

I think there is some evidence for believing that it arose at both sites.

This is a higher powered view of this same area, and there are a number of mitotic figures in this section. This, I think, is unquestionably malignant. These are normal glands along the side.

Well I mustn't take too long. I probably have taken too long already. But this is the sort of experimental work that seems to me to be worth pursuing. I don't say that this proves that heated fats are carcinogenic, but I think it makes out a prima facie case against any organic substances heated to 350° or more, as a possible source of carcinogen, and I believe that all the sources of organic matter heated to that temperature, to which we subject our stomachs, ought to be made the subject of intensive study.

Just one last word on the question of how valuable is evidence on the absence of known carcinogens from substances like heated fat. I asked Dr. Kirby to examine samples of heated fats to see if he could find any evidence at all, spectroscopic or other physical evidence, of the presence of any known carcinogen, and he assured me that there was no trace of any known carcinogen.

I then went into the question of how many molecules of carcinogens are necessary before you can detect them. The smallest quantity of any carcinogen on record as having caused a tumor, I think, was 0.4 γ, 0.4 of a thousandth of a milligram, which caused sarcoma in subcutaneous tissue of a mouse, reported by Shear. I asked Dr. Badger how many molecules would be present in this 0.4 γ, and I was rather astonished when he worked it out. I have it calculated here if anybody is amused by that sort of thing. In round figures, one thousand million million molecules were present in this 0.4 γ, and that is the sort of quantity which is hard to detect in an animal as small as a mouse. So I think that the fact that one can't detect any carcinogen in an extract or in any kind of substance which is biologically shown to be carcinogenic doesn't necessarily mean that it doesn't contain more than the smallest detectable amount, but there might still be several million molecules present and undetectable.

Bearing that sort of thing in mind, I suggest that we ought to be more careful than we are about what we quite habitually put in our stomachs, and I do think the present-day habit of coloring and flavoring foods with all kinds of synthetic dyes is a thoroughly bad one. Although it might mean that the people who make these things would lose some money, I would cheerfully face that risk if we could eliminate from our food all synthetic dyes and synthetic chemicals for whatever reason they are added. They can't possibly have any real value, and they might be dangerous. Two examples should emphasize that: Butter yellow (*N,N* dimethyl-*p*-aminoazobenzene) is undoubtedly carcinogenic and was presumably developed for the purpose of coloring butter. And the substance 2-acetylaminofluorene, which was going to be introduced as an insecticide, is one of the best carcinogens at the present time.

I think there would be a case for deliberate attempts at present for banning synthetic chemicals of any kind from any kind of food or drink.

Chairman Spencer: Thank you, Dr. Peacock. The next speaker, Dr. Walter Palmer, of the University of Chicago.

Dr. Palmer: I shall not attempt to discuss all the points raised by Dr. Ivy. I do wish to emphasize first the importance of continuing the studies of the carcinogenic agents, discussed so well yesterday by Dr. Strong, Dr. Stewart, and others, and by Dr. Peacock this morning. We should bear in mind that there aren't very many men in the world doing these studies or in a position to do them, and hence they should be supported to the full. The experiments are time-consuming, costly, and most important. The work on the genetic factor is certainly a most alluring approach to the problem, but as Dr. Peacock pointed out this morning, there is much to be learned from relatively simple studies with various carcinogenic agents. It is important to proceed with such studies not only in mice but also in the higher animals, monkeys, dogs, and perhaps horses, as Dr. Peacock suggested this morning. One of my associates, Dr. Klein, some years ago did carry out some studies with dogs; we were unable to produce carcinoma. Perhaps we didn't use sufficient doses of the carcinogenic agents or give them the right way or for a long enough period.

There is much to be learned, too, from further pathologic studies of human gastric cancer. It may be that although we are speaking of gastric cancer in this symposium as an entity, there are different gastric cancers. There are certainly different types of gastric cancer, tumors which behave differently as we all know.

Of course, efforts toward earlier diagnosis should be continued. X-ray and gastroscopic examination should be as routine as is feasible. One of the questions Dr. Ivy raised this morning is how feasible it is to X-ray or gastroscope periodically the entire population above 40 or above 45. I think one of the difficulties, a greater difficulty than the mechanical one of examination itself, is that of getting the people in to be examined. I believe enough young men could be found to do fluoroscopic examinations if some sort of a system were set up for a rapid fluoroscopic examination, so that it would not be necessary to rely simply on films, if there were some way of financing it, and if there were some way of getting the people in for

the examination. It seems apparent that all patients with pernicious anemia and all patients with anacidity and all patients with dyspepsia should be subject to such studies as often as possible. However, it seems clear to me that early diagnosis of all gastric cancers is an unattainable goal because even with our best efforts we won't be able to get the patients in during the latent period to which Dr. Peacock referred this morning, when there are no symptoms.

Another problem is that of the biologic characteristic of the tumor. In other words, many of these tumors begin as very malignant ones and metastasize rapidly and early.

In regard to treatment, we must bear in mind, of course, that the only progress really made to date in the treatment of gastric cancer is radical resection, and that progress is considerable. More studies, perhaps, should be made of the value of X-ray or other types of radiation therapy in the treatment of gastric cancer. At the moment this seems a rather futile and discouraging approach, but perhaps something will come of it eventually.

Dr. Ivy referred to the desirability of cancer registration. I think that it is worth while, but I should like to suggest that perhaps we ought to go a little farther than that and make an effort to find out exactly what is happening the country over, or in any one metropolitan area, let us say, to all the patients with gastric cancer. To report what happens at the Mayo Clinic, or the Memorial Hospital, or the University of Minnesota, or here doesn't really tell us what is happening the country over. It would be important to know the total picture of gastric cancer in any one area. For instance, in Chicago there are about a thousand deaths from gastric cancer per year. That is about 20 deaths per week. How many of these patients have been subjected to operation? How many have been X-rayed? How many have been autopsied?

I have wondered if it wouldn't be worth while for the United States Public Health Service to get up some sort of a team of half a dozen workers, maybe two or three doctors and social-service workers, to come into a city such as Chicago and go to every hospital in the city, get the cooperation of the hospital staff, get the cooperation of the Chicago Medical Society, study each person dying from gastric cancer, and find out all these things. At the end of a year we should know the true status of gastric cancer for that year.

One of my associates, Dr. Maimon, studied the cases of gastric cancer in the University of Chicago Clinics since 1927, and I should like to show you some of the findings. The rapidity of the rate of increase in the incidence of gastric cancer with advancing age was rather surprising to me, three-fourths of the deaths being in patients above 50. The ratio of male to female was 2:1.

Of some importance with regard to the duration of symptoms is the fact that prior to 1938 patients with symptoms of from 1 to 3 months' duration constituted 24.5 percent of the group and those with symptoms of 3 to 6 months, 18 percent. From 1939 to 1944 there was a slight but nevertheless appreciable increase in patients with symptoms of less than 6 months' duration, as seen in the first two columns of table 1, and conversely the number of patients who had had symptoms for over 1 year was less in this second 5-year period. It seems to us that this suggests a trend toward earlier diagnosis.

TABLE 1.—*Duration of symptoms in patients with gastric cancer in the University of Chicago clinic 1927–44*

Periods covered by analysis	Patients	Duration of symptoms in months				
		1-3	3-6	6-12	12-24	Over 24
	Number	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*
1927–38	293	24.5	18	26.2	11.9	19.1
1939–44	266	28.9	24.8	25.9	10.1	10.1

In studying operability and resectability of the total of 566 patients, 100 came in for gastroscopic examinations only, or diagnosis only, or refused the advice given, leaving a group of 466 who followed the physician's recommendation. Operation was not advised in 77 cases because of proved or definite distant metastases; I think we would all agree that the chief contraindication to operation is the presence of proved distant metastases. Operation was advised and carried out in 389. Resection was performed in 43.5 percent of the total of 466; 32.8 percent survived resection. This one-third, approximately, of 466, included the patients who had a chance of surviving 5 years.

As Dr. Wangensteen brought out yesterday, operability continues to increase and the mortality to decrease. Our surgeons are definitely of the opinion that these figures are already obsolete. The results in the last 2 years have been better than in the preceding years. From 1929 to 1939, the operative mortality was 22.6 percent; in the next 5-year period, 16.3 percent; and in the last 2 years still lower, in spite of the fact that in 25 percent of these operations other viscera involved by metastases were removed.

A group of 377 patients who had been operated on prior to 1941 were studied. Resection was carried out in 41.5 percent of the total; 30 percent survived resection; these then were the possible 5-year cures. Of the 115 who survived resection, we were able to trace 92; 28, or 7.4 percent, of the original group were alive 5 years later. Most of

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those who died in the 5-year period died in the first or second year.

There isn't much difference between the original series and the group of 5-year survivors with respect to duration of symptoms at the time when the diagnosis was made. Fifty percent of the 5-year survivors when first seen had had symptoms of more than 1 year's duration; 30 percent had had symptoms for more than 2 years. This suggests that a fundamental difference in the type of tumor is the determining factor in prognosis and longevity. This concept is further supported by the fact that 26.6 percent of the 5-year survivors had a palpable tumor mass when first seen. It also fits with the fact that there is no definite relationship between the size of the tumor and survival. In other words, survival may relate primarily to the biologic characteristic of the tumor.

A study of the survivors with respect to the Borrmann classification is shown in table 2. The second column shows the incidence of the various types of gastric cancer, the polypoid type (2.9 percent); the ulcerating but nevertheless localized type (17.6 percent); the infiltrative type with ulceration (16.3 percent); and more extensive infiltration (63.2 percent).

On the other hand, half of the 30 5-year survivors had carcinomas of Borrmann type I, and 13 had carcinomas of the Borrmann type II. There were no survivors in the Bormann class IV, the common type of gastric cancer.

TABLE 2.—*Relation of type of tumor to 5-year survival*

Gross classification of gastric carcinoma, according to Borrmann	Incidence in all gastric carcinomas	Incidence in 30 5-year survivors	
	Percent	*Number*	*Percent*
Type I	2.9	15	50
Type II	17.6	13	43.3
Type III	16.3	2	6.66
Type IV	63.2	0	0

Dr. Rigler commented yesterday on the fact that in pernicious anemia the majority of the carcinomas are of the polypoid type. Achlorhydria is a much more constant feature in this type than it is in the ulcerative types. I suspect that this fact explains the discrepancy Dr. Berkson mentioned yesterday. The longer survival may be due to a larger percentage of polypoid tumors.

There is 1 additional point that I might make with regard to these studies. Dr. Maimon went over the 577 cases to see if any of them had a proved duodenal ulcer and found only 1 questionable incidence, Dr. Ivy. However, in the past 3 months, Dr. Phemister has resected a carcinoma of the fundus of the stomach in a patient who 7 years ago had a duodenal ulcer and who still has a classic ulcer deformity of the duodenal bulb.

Dr. Steiner has studied the pathologic features of the tumors present in the 5-year survivors, and I hope that he will discuss them.

In summary then, our knowledge of gastric cancer is great, and our ignorance greater still. We need more knowledge in every phase of the problem; we need to know more about the genetic factor; we need to know more about the effect of carcinogens on mice and on higher animals; we need to know more about the pathologic and clinical characteristics of human cancer; and we need to know more about the resistance of the host, because after all there is such a thing as resistance to carcinoma, even in the human being. It would be very helpful, also, if we possessed reliable information on just how early gastric cancer is being diagnosed throughout the United States, how it is being treated, and with what success.

Chairman Spencer: Before we throw the meeting open to general discussion, I am going to ask Dr. Schindler to discuss the relationship of chronic gastritis to gastric cancer.

Dr. Schindler (College of Medical Evangelists, Los Angeles): I believe that Rigler and Kaplan were the first to discover systematically beginning gastric carcinomas. They proved statistically the increased frequency of gastric carcinoma in pernicious anemia, and they drew the practical consequences with a success which to my mind is sensational.

Yesterday Dr. Rigler did not clearly commit himself. But in the original publication the authors assumed that the atrophic gastritis of pernicious anemia was not the cause of the cancer formation. This assumption, in my opinion, is not correct. Rigler and Kaplan were impressed, it seems, by the statement made by pathologists that older people regularly have some atrophic gastritis. It will not be denied that in older people, who have had many attacks of acute gastritis, occasional accumulations of lymphocytes and some intestinal islands may be found. Yet there is no comparison between the aspect, the gross aspect, I mean, of the stomach of the average healthy adult and the stomach seen in pernicious anemia and in many cases of gastric carcinoma. The quantity of the alterations of the mucosa is decisive.

This can well be shown by a survey of stomachs in which benign adenomas have developed. These pea- and bean-sized tumors cannot possibly cause atrophic gastritis; yet they are much more frequently found in stomachs with grossly, I mean gastroscopically, visible gastritis than in stomachs with apparently normal mucosa. The incidence of benign gastric adenomas is given in table 1.

TABLE 1.—*Incidence of benign gastric adenomas*

Group	Number of cases	Number of adenomas	Percentage
All patients	2,167	36	1.65
Patients without atrophic gastritis	1,814	15	.83
Patients with atrophic gastritis	333	21	6.0
Patients with uncomplicated atrophic gastritis	310	15	4.8
Patients with pernicious anemia	43	6	14.0

The difference between the pernicious anemia cases and cases of uncomplicated atrophic gastritis is remarkable. What causes this difference? It is best explained by the extent of atrophic changes. In pernicious anemia, we usually see extensive atrophic changes. In the group of uncomplicated atrophic gastritis, many cases were listed which had only small patches of atrophy. If Warren and Meissner are right that the epithelium in atrophic gastritis corresponds to precancerous conditions in other organs, then a greater number of such precancerous elements should produce a greater number of tumors. The difference between apparently healthy stomachs and those with some visible atrophic gastritis but without pernicious anemia is still considerable. It is a relation of almost 1 to 5. What is valid for benign tumors (where we can prove it) should be valid for malignant tumors (where we cannot prove it) also. I believe, therefore, that the frequency of gastric cancer in pernicious anemia is due to the extensive atrophic gastritis present.

Although many years will elapse until we can prove conclusively that uncomplicated atrophic gastritis is a precursor of gastric carcinoma also, we should not be deterred from the only procedure which promises the discovery of small gastric carcinomas, namely, the frequent examination of patients suffering from atrophic gastritis, with and without anacidity.

How can this be accomplished? It is easy in private gastroenterologic practice and in gastroenterologic departments. The dyspeptic patient in whom nothing was found at X-ray examination always insists on gastroscopy, and thus the sufferers from atrophic gastritis, about 12 or 15 percent, are discovered. It would not be feasible, in my opinion, to re-examine routinely every dyspeptic, as Rigler and Kaplan did their patients with pernicious anemia. But it can be done in the relatively small group with atrophic gastritis. These frequent rechecks, to be continued if the patients become symptom-free, should be undertaken not by gastroscopy, but by the X-ray relief method, four to six films taken in one row (that goes very quickly and in a few minutes), and I think that rarely a small carcinoma will be overlooked by this method, whereas the method of complete filming will not reveal small beginning tumors.

What Rigler and Kaplan accomplished in pernicious anemia may then be accomplished in the larger group of uncomplicated atrophic gastritis, namely, the systematic discovery of very small, beginning, no-symptom-producing gastric carcinomas.

Finally, I want to say that I was very glad that Dr. Palmer brought up the different gross types of gastric carcinoma and their different prognosis.

Chairman Spencer: Thank you, Dr. Schindler. I trust that the discussion will continue on the same level as yesterday afternoon. There is no reason why anyone should pull his punches at all, because as you very well know, the very heart and soul of progress lies in the clash of opinion. Is Dr. Rigler here?

Dr. Rigler: We have been giving a great deal of thought to the question how one can proceed to make X-ray examinations of many individuals who have no symptoms. I might ask who in this room over the age of 50 has had a gastrointestinal examination. I am sure I shouldn't get very many affirmative answers; and if we don't do it, you can well imagine how difficult it is to get patients to do it. In fact, if I asked who in this room has had a film of the chest every year, I anticipate that I shouldn't get very many affirmative answers, despite the tremendous propaganda the United States Public Health Service has conducted.

So the imponderables here are very, very serious. We have found that in this pernicious-anemia group, for instance, where we have offered the examination free (we feel justified in saying to this group, "You are in danger of having a carcinoma of the stomach"), it is like pulling teeth to get patients to come back every 6 months for an examination. I am sure that any effort is going to be met with that kind of difficulty. If you impose a screen, as we have, by doing a gastric analysis, the difficulties are multiplied extraordinarily; and as I think you saw from Dr. State's figures, we were unable to get more than 50 percent of the patients to have a gastric analysis done. That loses half of your patients right off the bat. Not only that, but the ones that you do a gastric analysis on aren't very much inclined to come back again unfortunately. And if that applies to gastric analysis, it applies much more so to gastroscopy. I could ask who in this room has had a gastroscopy done on himself, and I am sure that I shouldn't get very many affirmative answers. I am sure that, too, is a very difficult thing; routine gastroscopy, the way we do it, tends to keep patients from coming back, and of course the crux of the matter is to see the patients often. If you don't, the whole program falls down, because in most cases you are not going to find carcinomas the first time you see these people.

In the pernicious-anemia group, for instance, we had many cases with negative diagnoses which became positive after a period of years, and that is going to happen in any such program.

There are a number of ways that one could proceed. I think we all should agree that the only feasible method for finding an early carcinoma that we know of at the present time, if you examine symptomless individuals, is by X-ray examination of one kind or another. That is the thing I think patients in our clinic, at least, resist the least. We lose some patients because we insist on their waiting around an hour and swallowing some unpleasant material, but we don't lose very many that way.

The problem, of course, is how to do this on a large scale without too much cost. I was thinking in terms of Dr. Swenson's work, for instance. I imagine that even a very free-spending government would be unwilling to spend all the money it would cost to examine 2,400 patients just to find 3 cases, and next year, when Senator Taft and Representative Knutson, from Minnesota, are doing the spending, I anticipate that we shall have even more difficulty. Those are other things that we must consider. Now there are a number of possibilities. One is that we do what Dr. Swenson did, that is, do fluoroscopic examination only (I think I am quoting him correctly) except in the cases that suggest there might be something abnormal.

In any case, that is a very expensive form of examination and entirely impractical at the present time on a very large scale. I think it is perfectly practical as a pilot sort of procedure, purely from the point of view of getting experience, as Dr. Swenson and his associates have already done. But it involves an expensive mechanism, the services of an experienced radiologist, and a lot of his time, all of which are almost impossible to obtain at present on any large scale.

Another thing would be to do what we are doing now, that is, take films and do a fluoroscopic examination, which is more expensive and more time-consuming, both on the part of the radiologist and on the part of the technician.

A third method would be to institute some type of quick filming which didn't require the presence of a radiologist at the time the patient was examined but would permit examination of a series of films at the radiologist's leisure within the next day or two. That is not simple, and most radiologists will rise up against it, because they are so used to doing fluoroscopy that they are unwilling to accept such a thing.

I was impressed by some equipment that Dr. De Castro, of São Paulo, showed me, with which he is able to take a large number of very small films by the photofluorographic method, indirect cineroentgenography, but it really isn't a motion-picture method because they are done very slowly. They use small films, which are enlarged for interpretation. The technician can by an indirect-mirror system see by a glance where the barium is at the time the films are made. It is relatively inexpensive from the film standpoint and doesn't take long. The patient may be examined in many different positions, and a very large number of films can be made. This procedure may permit (and I say "may" advisedly; because I don't think it has ever been tried, and there are handicaps which every experienced roentgenologist can think of) examination of very large numbers of individuals.

My impression is that we ought to establish five or six different procedures, well-controlled, to see what happens under such varying circumstances. In any case, it is not a fruitful field. As one can note from some of the statistics on the board, regardless of what you do, the number of cases discovered will be relatively few. Unless some easy sieve were put into the process, as we found with pernicious anemia, you are going to find that you are doing an enormous amount of work to discover a very small number of cases.

Dr. E. V. Cowary (St. Louis): I did not come to this conference prepared to speak, but the discussion has been so stimulating that I venture to express my ideas. The work reported has been on a broad basis and has included many profitable lines of investigation. Yet there is an aspect of the problem of gastric cancer which has not, in my opinion, been adequately considered, that is, the conditions of cell life in the gastric mucosa that antedate the localized malignant transformation of cells therein.

Many methods of chemical analysis are now available, applicable to small amounts of tissue, which, if used, could supply data on enzyme activity, water content, lipids, minerals, and so on. These data would help us to understand to some extent the conditions under which the cells are living.

Atrophy of the mucosa is frequently mentioned as preliminary to cancer development in it. We ask ourselves, Of what does this atrophy consist? The word "atrophy" implies a wasting of the tissue, perhaps a loss or decrease in something. Such chemical studies might reveal a deficiency or a whole flock of deficiencies.

We hear a lot about carcinogens. Some living cells exposed to them become malignant after a considerable lapse of time, if the conditions, but little understood, favor the transformation. Surely it is our task to find out how the living conditions of the cells of the gastric mucous membrane in so-called precancerous states differ from those normally existing.

In our own studies on epidermal carcinogenesis, we find that a deficiency in many components exists in the epidermis for a considerable length of time before the malignant transformation takes place. We are inclined to think, in terms of Dr. Spencer's views on the subject, of this transformation as a survival mechanism operating occasionally in cells subjected to adverse living conditions. The adverse conditions, or deficiencies, if any, in the mucous membrane of patients with atrophic gastritis may of course be entirely different from those in the epidermis, exposed as it is rather more directly to the outside world and thus to external carcinogens.

Therefore in any detailed, comprehensive study of gastric cancer, I want to plead for a systematic investigation of the conditions of cell life in the gastric mucosa. I believe that this is feasible, far more feasible than most of us realize, owing to these new techniques. It is worth while in human mucosa and still more desirable in the gastric mucosa of animals subjected to experimental carcinogenesis and of strains of mice especially prone to gastric cancer. Let us get at gastric cancer by studying the conditions of cell life where the malignant change takes place. Perhaps some of these conditions can be corrected. At least, until we know what they are, we can't say that they cannot be corrected.

Chairman Spencer: Dr. Templeton, of Seattle, Wash., has to catch a plane, so I am going to give him the privilege of speaking next.

Dr. Templeton: I think we are all agreed that we do not know what the results of a mass survey for gastric cancer by X-ray would be. As St. John, Swenson, and Harvey have indicated, certain information can be obtained. Dr. Rigler has presented certain proposals for conducting a survey, and I should like to elaborate on his proposals.

About 3 years ago I went to the Cleveland Clinic. We were short of trained personnel and had a large number of gastrointestinal examinations to perform. It was impossible to spend much time fluoroscoping the patients. Furthermore, I was convinced that all lesions cannot be seen at fluoroscopy. Small gastric ulcers are easily overlooked or cannot be seen. When I worked at the University of Chicago with Drs. Schindler and Palmer, I experienced considerable trouble visualizing certain small gastric carcinomas whose location I knew from looking through the gastroscope with Dr. Schindler.

It seems to me that using films has a lot to offer, and I propose a method which I think may be as accurate as fluoroscopy alone. When I was at Cleveland, I had a group of inexperienced young men. I couldn't do all the fluoroscopies myself, and I couldn't depend entirely upon their fluoroscopic findings. I had to check their observations with films. By taking a series of films in positions I shall describe later, I think I was able to exert a reasonably accurate control over their work. If the films did not tell the story, the patients were brought back, and I re-examined them by using both fluoroscopy and spot films.

By using films without fluoroscopy, I think a large number of patients can be cataloged right at the start. Either they do have a lesion or they don't have a lesion. If there is a question of a lesion or if the films are inadequate, the patient returns for a more detailed examination, the spot machine and the mucosal relief method being used, as Dr. Schindler stated. There is going to be a certain percentage of error; that cannot be avoided. It occurs in the tuberculosis survey. We can, I think, keep it low by feeling our way and changing our techniques as errors creep in.

In selecting the patients for sampling, a group, probably in some factory where the majority of employees are over 40 years of age and can be re-examined at the end of 1 year, might prove satisfactory. Re-examination should be done within 9 months to 1 year, because it is known that most of the deaths occur within this period. If a 2-year interval is selected, lesions may be overlooked, because the cancer can start 6 months after the initial examination and the patient die before the next examination. By studying statistics, I think a satisfactory interval between the examinations can be determined.

The method which I want to propose and which I think can be done rapidly makes use of the miniature film. The exposures are all made with the patient lying on the table. Beneath the table is the reciprocating grid developed by Hodges and Morgan. The grid saves time in that it is unnecessary to recock it every time an exposure is made. Beneath the grid is a housing fitted with a screen and a Fairchild 70-mm. camera, similar to that used in the photofluoroscopic machine for the mass survey of the chest. Roll films are used because these films are more readily read than the cut film. The machine should be equipped with a Morgan-Hodges timer, which reduces to a minimum the bad films from poor exposure. The technical part of the examination can be carried out by a trained technician without the aid of a physician.

It is very important that the examination be carried out in a definite sequence. The fasting, standing patient is given a drink of barium mixed with water to the consistency of thick cream, about one-half barium sulfate powder and one-half water by volume. The barium coats the lower part of the stomach, and the air normally in the stomach gathers in the upper portion. Three exposures are now made with the patient in a horizontal position. The first exposure is made with the patient lying

on his back and turned slightly to his left side. This position causes the barium to flow from the antrum into the fundus, and air present in the fundus rises to the antrum. In a majority of instances, an excellent air-mucosa relief view of the antrum is obtained. The fundus distended with barium mixture can also be observed.

The second exposure is made after the patient is turned prone. The air in the antrum now rises into the fundus, which produces a normal air-mucosa relief of that structure. The antrum distends with the barium mixture.

The third exposure is made by turning the patient from the prone position to a half-right lateral position. This position gives an oblique view of the lesser curvature. By combining these three views, a good idea of the mucosa relief, as well as of the stomach distended with barium, is obtained in a high percentage of the examinations. Thank you.

Dr. Laszlo: I was much impressed by Dr. Cowdry's remarks and agree with him that it is wise to shift research from the problem of achlorhydria to some less known enzymatic functions of the stomach cells. We all agree that in the age group of maximum cancer incidence atrophic gastritis is more frequent than it is in the younger age groups. The question then arises, What possible significance may this increased frequency of atrophic gastritis have for the development of cancers? In the following, I shall attempt to outline briefly an approach, which appears to have some hopes for success.

For a number of years the group I was associated with studied the factors that inhibit tumor growth. In 1945 at the meeting of the A. A. A. S. at Gibson Island, I reported some of these experiments. As we all know, normal cells will not multiply unless supplied with all the nutrients, minerals, and growth factors. The same appears to hold true for malignant growth; tumor tissues will grow optimally only if these factors are abundantly supplied. However, in studying the requirements of tumor transplants on growth factors, we found two such, which, though promoters of normal growth, are inhibitors of malignant growth. These two substances are inositol and folic acid. We also described a number of substances related to the growth factor-x "vitamers" which were also inhibitors of tumor growth.

Natural food substances, such as grains, were also found to contain tumor-growth-inhibitory factors. Their liberation from the bound into the free compounds is probably an important partial function of the intestinal tract. I therefore wonder whether atrophic gastritis, which occurs at the highest incidence in the age groups at which malignancies are at the highest rate too, might not create a situation in which the liberation and utilization of these inhibitors in the foods is impaired.

Dr. E. L. Howes (Columbia University): I should just like to mention a control of laboratory experiments that has not been fully considered in these discussions, namely, the relationship of the integrity of the gastric mucosa to diet and to injury. The history of our awareness of this relationship is most constructive. Fibiger back in the early 1900's discovered that some of his laboratory rats had developed carcinomas of the stomach. Many of the pictures of tumors shown yesterday are practically identical with his original illustrations. He found associated with these tumors numerous ulcerations of the rumen and pyloric portions of the stomach. Searching for the cause of these new growths, Fibiger examined a great many wild rats to determine whether they had similar lesions of the stomach. They had neither tumors nor ulcerations of the stomach, and therefore he believed that the cockroaches that they had eaten in the laboratory accounted for the formation of the tumors. He proceeded to produce the lesions, both ulcerative and proliferative, by feeding ground-up and dried cockroaches. Fibiger got a Nobel prize for this work.

Beginning at this point, the search for the cause of these ulcerations and their subsequent proliferation has been long. Many investigators have tried to find the changes in diet that cause them and how to make them more extensive. Only a few can be mentioned: Pappenheimer and Larimore, at Columbia University; Carlson here at Chicago; Buchner and Konjetzny, in Germany; I spent 2 years on them; and finally Zuchner and Berg have spent nearly 10 years and are still studying them.

When the dietary deficiency occurs, both the glandular mucosa of the stomach and the squamous epithelium in the rumen portion are damaged. At first ulcers form, the surrounding area is infiltrated with lymphocytes, and then in the presence of irritation a remarkable overgrowth of epithelium takes place. Even mechanical irritation, such as is furnished by hair or steel filings or cockroach shells, causes proliferation, and this effect must be enhanced by chemical irritation. Adenomas form; and if a break occurs in the muscularis mucosa, the epithelium grows down through it to resemble a malignant tumor.

Microscopically, the epithelium that proliferates does not contain either pepsin or acid-secreting cells. It is the so-called intestinal type. Incidentally, this is the type found in carcinoma of the stomach. Because it is a precancerous change, the next important step is to study what happens to the normal enzymes of the stomach after this change has taken place. Acidity cannot be talked about, but the amount of hydrochloric acid. Normal glandular epithelium secretes hydrochloric

acid, while in cancer of the stomach decomposition acids are formed, especially lactic acid. Pepsin secretion also should be altered.

The mechanism of formation of this intestinalized epithelium has become apparent to me only since I have begun experiments on producing adenocarcinomas of the stomach by means of carcinogenic threads. Artificial sinuses have been made by leading these threads down through the muscularis mucosa. The superficial mucosal secreting cells are the ones that move down to line the sinuses and proliferate, and this transformation is purely a reaction to injury. With this background, it is possible, in experimental animals with changes in the mucosa as a result of changes in diet and with breaks in the muscularis mucosa resulting from injury or lymphatic infiltration, to obtain all sorts of proliferative distortions of epithelium yet not a malignant new growth.

The dietary deficiency initiating changes in the lining of the stomach is very subtle because inanition and failure to consume food always complicate the picture. In fact, only two things have been found to prevent formation of ulcers in the acid-secreting and rumen portions of the stomach, namely, whole B complex and feces. Lastly, Zuchner and Berg believe that ulcers that form in the prepyloric area of the stomach, that is, in the normally "intestinalized" epithelium, result from chronic deficiency of calcium from inadequate intake. Animals do not always begin to eat feces until they develop ulcerations; but if they are fed feces, ulcerations are prevented. It will be recalled that some of the lesions did not form under crowded laboratory conditions whereas they did so when the animals were separated. Under crowded conditions, the animals have a better opportunity to eat feces. Moreover, in regard to the stomachs of the monkeys exhibited yesterday, it will be recalled that on fog oil the monkeys lost weight and did not eat. These are just two possible circumstances where a change in the diet was possible that could affect the integrity of the gastric mucosa.

Dr. Catharine Macfarlane (Woman's Medical College, Philadelphia): As a gynecologist and on the basis of a cancer-detection experiment conducted at the Woman's Medical College since 1938, I am of the opinion that an individual whose relatives died of cancer of the stomach would offer very little resistance to any method of periodic examination for the detection of cancer in an early stage. We find in Philadelphia that the public is much more eager to have periodic examinations than the medical profession is willing to make them.

Dr. H. D. Harvey (Columbian-Presbyterian Medical Center): I should like to sketch very briefly for you the background which induced Dr. St. John, Dr. Swenson, and me to take up the study of the so-called normal stomach in the hope of finding gastric carcinoma. I am speaking now of the clinical approach and not at all of the laboratory.

Prior to 1935 our 5-year arrest rate in carcinoma of the stomach was 2 percent. Around 1935 we began to get especially interested in the subject of treating gastric carcinoma. We had excellent X-ray assistance. Dr. St. John and I went to the clinic personnel and spread the gospel as much as we could, of picking up early symptoms, particularly in people over 50. The result of all our efforts has been this, that in the years between 1935 and 1940 the arrest rate has risen to 6 percent. That is a threefold increase, but after all it is not a very large dent in the death rate of people with gastric carcinoma.

Now why did we go no further? Why could we not succeed? In studying the records, as far as we could tell, the reason why we could not be more successful in our operations was simply this, that people generally did not come to the hospital in time for a curative operation. Their symptoms were so mild and so insidious that they did not seek medical aid until they were hopelessly incurable. That is a statement I cannot prove, but that is the impression we got out of studying the records. In view of that, it became apparent that if the patient wouldn't come to the doctor in time, the doctor had to get to the patient before he knew he was sick, and that is why we attempted the study of people, who under normal circumstances would not have come to us because they had gastric symptoms. The first group of cases that we studied were people who came to the hospital for conditions other than digestive complaints.

Let me interpose here the counterbalancing, optimistic side of the picture. Certainly a loss of 94 percent of our patients was not optimistic, but it is also true—and this fact should be emphasized clearly as much as the pessimistic side—that among the group who came to us before they had metastases and who survived resection, the 5-year-arrest rate was 50 percent. Dr. Howard Gray, at the Mayo Clinic, with their large series of cases, wrote me that their figure in that group is practically the same. In other words, if you get gastric carcinoma before it has metastasized or before you can find metastasis, you may expect a very high arrest rate.

We felt, therefore, from two points of view that it was essential, if we were to make inroads on the death rate of cases of gastric carcinoma, that some screening method be set up to be applied to people before they knew they had anything the matter with them. We balanced in our minds the various methods of setting up the screening program, and it seems to us the quickest, most direct,

and simplest program was the one we adopted. Of course, it is an expensive, cumbersome method of trying to study a large group of people. I hope sincerely that some better method will evolve.

At present I feel that it is up to the X-ray men to devise the best method of study. We should like to go ahead with our present study. The cost of the study must, I think, be weighed against the cost of the 94 percent of patients who are now treated unsuccessfully. The man-hours which have gone into treating 94 percent of the cases of gastric carcinoma that come to us reach astronomic proportions. What we hope to do is to take some of that effort which saves not a single life in that group and put it to early discovery. We picked up three malignant cases, two of which were carcinomas that had no metastasis. I saw them just a month ago. These people are now 4 years postoperative and are perfectly well.

Dr. Kaplan: I want to pass on a suggestion that has reached me. Ordinarily we are inhibited in a clinical investigation by our inability to carry out on willing human subjects the experimental procedures that seem indicated to us, and it seems to me that we are now being presented with a growing group of patients upon whom an experimental procedure is being made for us. I am referring to the operation of vagotomy for the treatment of peptic ulcer, which was popularized here by Dr. Dragstedt and which is apparently meeting with approval by surgeons all over the country. If the operation continues to take hold, increasing numbers of patients are going to be subjected to vagotomy; and as I understand it, the secretion of hydrochloric acid will be seriously reduced over a long period, in those patients.

If we are serious in the belief that chronic achlorhydria is related to the development of gastric cancer, it would seem reasonable to set aside these vagotomy patients, perhaps to include them in a registry such as Dr. Ivy suggested, and follow them clinically with repeated 6-month X-ray examinations, to determine whether the incidence of gastric cancer in this group is any higher than in nonvagotomized controls.

Dr. Figge: I have several comments to make that have to do with our general attitude towards how much we want to spend on this and how much on that. It has to do with whether or not we want to go off the deep end by attempting to detect and treat cancer according to the present state of our knowledge or whether we want to concentrate more effort on finding the cause and methods of preventing cancer.

If we limit our attempts to detect cancer to the cancer-age group, there are 47 million people in the United States over 40 years of age. Those of you who are working in these cancer-prevention clinics, as they are called—cancer-detection would be better—know that in 1 of these clinics you can examine, with the detail that you use, only a thousand people a year, if you examine them twice a year. This would mean that in this country we should have to have 47,000 such clinics. If it costs approximately $5 an examination, either to the patient or to whoever is supporting this, it would require $470,000,000 to do the job, to say nothing of the time, energy, and personnel. Moreover, these examinations would have to be made year after year. It is temporizing, so to speak, and while it would be very valuable to gather statistics, I think it should be done in a conservative, limited way, and we should spend our main effort along the lines of basic research advocated by Dr. Ivy, Dr. Cowdry, and others.

I have one item to add to some of the lines that might be investigated, and a little caution with regard to what may happen in these cancer-detection clinics in the long run. A short time ago I heard a paper about a man, who might be called a "cancerophobe." About 1927 this man thought he was developing cancer of the stomach so he went to a gastroenterologist and had an examination. The doctor took adequate X-ray pictures and told him he didn't have a cancer. The man doubted the doctor so he went to the Mayo Clinic where another series of X-rays was taken. He spent the next 10 years having an average of three examinations a year in different places, being X-rayed all the time. He stopped for a short time but continued this activity after 1940, and in 1942 it was discovered that he had an inoperable cancer of the stomach. At the time I heard this paper, I wondered whether all the X-ray examinations hadn't helped to induce the tumor. Perhaps if he had paid no attention to the possibility of cancer he might still be living.

The item I want to suggest as another line of attack on the gastric-cancer problem would be to investigate the psychogenic aspect of this disease. This suggestion is hesitatingly made; but in view of the psychogenic factors involved in acid secretion, it may have possibilities.

The statistics on 5-year survivals also deserve comment. We are told that 90 to 94 percent of the patients with operable cancer of the stomach die, but the cause of death in this group is not stated specifically. Certainly if they die of pneumonia it should be taken into account in the statistics. I assume that most of these people die of the neoplastic disease, but those of us who are not clinicians should not be left to wonder.

This brings to mind another feature of this cancer-detection program that deserves open discussion. It seems to me that we are really neglecting the most important group. This may hurt some of the older people, but I feel free to say this because I am in the group above 40. This group is

really not the important group either to save or to study. Some of these older people that we intend to examine will be saved from cancer and perhaps will have a 5-year survival. They are going to survive—for what? To die of something else. It seems to me that we ought to put more emphasis on the group below 40 that still have their lives to live. Moreover, the etiologic factors that induce cancer probably precede the development of malignancy 15–20 years. If we are interested in utilizing the cancer-detection clinics to discover these etiologic factors, we must concentrate more effort on the studies of conditions in the younger groups.

Failure to recognize the ultimate limitations of an all-out colossal indulgence in cancer-detection clinics might well prevent us from realizing the great possibilities for discovery that these clinics on a smaller scale would present. The chief disadvantage of such overindulgence would be that we might soon find such a high proportion of our time and money expended in the direction of cancer detection that basic investigations would go begging.

Dr. Warren: There are several unrelated points that I should like to mention briefly, that have been brought out in the various discussions and deserve re-emphasis. Before that, however, I should like to take issue with Dr. Figge. It seems to me that a group of this sort ought primarily to be concerned with deciding what avenues of approach to the gastric-cancer problem offer any chance of hope. It is up to those who hold the purse strings to decide whether they will give money for it. I think we ought to ask for anything that we think is worth while, regardless of the money involved. Then let those individuals who have generous impulses decide whether or not they feel like supporting it. I think if we start screening what is worth while or not worth while too much from the standpoint of cost, we may overlook some valuable bets.

There is one fundamental principle in pathology that has been indirectly touched on a number of times in the discussion here; that is, that it is extraordinary for neoplasia to occur in healthy tissue. Just as we find that in those individuals with pernicious anemia, with various types of changes in the gastric mucosa, there seems to be an increase in gastric cancer which is following out the changes we note in the endometrium, for example, while normal function is going on, and there is virtually no chance of development of endometrial carcinoma. It is only after atrophic or degenerative changes have set in in the endometrium that we have carcinoma developing from it.

I was particularly interested in Dr. Palmer's diagram because it re-emphasized another of the fundamental principles of pathology, which up until recently the exogenesis of surgical procedure, surgical technique, had forced those attempting to treat gastric cancer to violate. You note that in Dr. Palmer's group of the Borrmann type IV, the infiltrating carcinoma, there were no cures. All too often I have had autopsy cases, persons on whom partial gastrectomies had been done, in whom the recurrence of the tumor that had brought about their deaths was in the remaining portion of the stomach. The surgeon who would take out two-thirds of the breast for a carcinoma of the breast would feel that he had not been dealing properly with his patient. I think it is very important to consider at least the advisability of more total gastrectomies than are done at present.

We should not overlook the splendid body of experimental human material that we have in individuals who have had different types of surgical procedures for nonmalignant conditions, carried out upon the stomach. If we are interested in the influence of bile on the gastric mucosa, for example, what could be better than a patient who had leukocytal gastrostoma? If we are interested in the effect of the absence of bile, what could be better than a patient with a gastroenterostomy and a partial resection? There are a great number of experimental procedures which can be very readily carried out by observations on persons of this type.

In the discussion of the radiographic study of these lesions, there is one point that I should like to mention, as a pathologist with a brotherly interest in radiology. That is, that there is no more risky procedure for the radiologist than fluoroscopy; and in the enthusiasm for finding early carcinoma, it should be kept in mind that fluoroscopy carried out day after day is the best way for a radiologist to exceed his tolerance dose.

Dr. Shay (*Temple University*): Dr. Palmer mentioned the question of differences in resistance of individuals to malignancy. Dr. Ivy, having in mind some of the things that have been discussed yesterday and today with regard to the duodenum, I was wondering if an attempt to measure differences in local-tissue resistance would not be worth consideration. The question of pH, by implication or directly, has been invoked with respect to gastric carcinoma. Whether the shift in pH towards the alkaline side (gastric anacidity) or whether merely a change in pH to which the tissues are not normally subjected is to be considered of importance, I do not know. If it is a matter of higher pH, the duodenum certainly houses such a pH regularly.

Too, regarding the possible role of gastritis in gastric malignancy, does not the high incidence of duodenal ulcer and the associated duodenitis subject the duodenum frequently to a similar pathologic state? Then there is the possible factor of carcinogens supplied by bile, which you and Dr. Peacock mentioned this morning. If there is a carcinogenic agent in bile and it plays a part in

gastric carcinoma through the regurgitation of duodenal contents into the stomach, the exposure of the duodenal mucosa to such a carcinogen on purely anatomic grounds should be even greater than that of the gastric mucosa.

The duodenal mucosa, therefore, is exposed more intensely than is the gastric mucosa to three of the factors: higher pH, duodenitis, and exposure to a carcinogen (?) in the bile, which have been stressed in their possible roles in gastric malignancy, yet we are all aware of the very low incidence of duodenal malignancy compared with that of the stomach. I wonder if an attempt could be made to establish a difference in the minimal amount of carcinogen injected that would produce carcinoma of the stomach and carcinoma of the duodenum.

Dr. Ivy: There can be little doubt regarding a difference in tissue susceptibility. When Dr. Lorenz and Dr. Stewart gave methylcholanthrene orally to rats, they failed to obtain cancer of the glandular stomach but did obtain cancer of the intestine.

Dr. Peacock: May I just answer that one point that was raised with regard to the bile in the duodenum? Of course, the point which perhaps I do not make clear is that bile is a good solvent for carcinogens as long as it is in an alkaline medium. When bile regurgitates into the stomach, even with people with achlorhydria, the pH is lower in the stomach than in the duodenum; and under these conditions, if you make a solution of carcinogens or hydroxy compounds that are formed by the liver and excreted in the bile and if you put such a solution into an acid pH, you get a change, a loss of fluorescence, and I suggest you might get a precipitation of the potentially carcinogenic material on the stomach side of the pylorus. That is my point, that the cancer is common on the acid side of the pylorus and extremely uncommon on the alkaline side, although the histology of the two sides is not very different. That is why I believe there is some reason to think that perhaps the effect of the acid on the bile might be significant.

Dr. Shay: Certainly acid gets into the proximal duodenum and so could cause precipitation of the carcinogen there. It should also be pointed out that in the anacid stomach the pH may reach a high figure—even greater than 8.0.

Dr. Cooper: A great deal has been said about experimental gastric cancer and the detection of the disease in patients without symptoms, but we haven't heard much about the diagnosis of gastric cancer in patients who have symptoms. This is the primary problem that faces the clinician, and I don't think this meeting should close without comment on this matter. I feel that any well-rounded program attacking gastric cancer should devote as much attention to diagnosis in those patients with symptoms as to basic research on etiology. For it may well be that the difficulties of diagnosis and cure will be with us long after the cause of the disease is clearly understood. If the accumulated Nation-wide statistics could be projected backward into the offices of thousands of doctors listening to the stories of untold thousands of patients with gastric symptoms, we should have some concept of the magnitude of the diagnostic problem. Which of these patients has gastric cancer? It is the clinician who knows how difficult it may be to answer this question.

At the outset it should be emphasized that most patients with gastric cancer have symptoms. They are vague and difficult to evaluate but are generally present. When the series at New York Hospital was studied, the average duration of symptoms before admission to the hospital was 12½ months, and 85 percent of the cases were inoperable. For an average of 8 months they failed to go to a doctor and treated their disease over the back fence or in the corner drug store because they were not very sick. For an average of 4½ months they were under a doctor's care. The patient's and doctor's delay in arriving at a diagnosis is reflected in the low operability and further in the dismal Nation-wide statistics. These are the figures that challenge us, and their reduction is the problem that faces us squarely.

A vigorous, uphill battle is being waged against patient delay by the American Cancer Society and similar organizations in public educational programs. In New York City we feel that real progress is being made. But too little is being done to educate the doctors, and the diagnostic aids he has available are often misleading. The X-ray is certainly the most useful diagnostic aid, yet it is not more than 80 percent accurate on the first examination. The gastric analysis is of real diagnostic significance in the presence of a gastric lesion. The free acid is low or absent in 85 percent of the known gastric cancers, yet is normal or even elevated in 15 percent. The use of the gastroscope has helped, particularly in supplementing the weak points of the X-ray examination. But new and better diagnostic methods are sorely needed, and doctors need to be educated in their use. It is in this direction and in the field of application of what is known that the door is most open to progress.

Dr. Cowdry: I am sorry for the clinicians! I want to say a word about something that they might do since they seem to feel a little bit out of it in this discussion. The spread of cancer may be related to the permeability of connective tissue, as you well know from the work of Duran-Reynals and others on the spreading factors and also when we recall the work of our Russian

friends with the ACS serum. I think that we ought to discover in cases of spreading cancer whether the permeability of connective tissue is increased by making the simple test of injecting trypan blue and measuring its spread.

Dr. Golden (Presbyterian Hospital): The question of accuracy of X-ray diagnosis of cancer of the stomach has been brought up by Dr. Ivy and Dr. Cooper. In the discussion of accuracy, do we mean accuracy in the detection of a lesion, of an abnormality in the stomach, or do we mean accuracy in our judgment whether an abnormality is probably cancer or not? In the majority of patients it is not too difficult to detect an abnormality. The problem is to determine whether the abnormality is cancer. The spastic antrum, of which we are seeing more and more, is an example. Has the patient a hypertrophy of the pyloric muscle and an antral gastritis or has he an infiltrating carcinoma? In an ulcer, is the excavation benign, or is carcinoma present? Yesterday I spoke of Dr. Stout's superficial spreading carcinoma and mentioned the fact that he has collected 28 of these cases in the last 9 years. Seven of the twenty-eight carcinomas were in the mucous membrane around a pre-existing, open, peptic ulcer. In 8 of the cases, the carcinoma developed in the mucous membrane covering the scar of a healed peptic ulcer.

Some surgeons say that if a reliable radiologist is not sure about the character of the lesion, or if he suspects that malignant disease may be present, an operation should be done. Operation on the basis of intelligent suspicion is necessary if we are going to get early carcinomas, but it is inevitable that some benign as well as malignant lesions will be found. In Dr. Swenson's series, which has been mentioned several times, abnormalities were detected in seven patients; all were operated upon but in four the lesions proved to be benign. That would give an accuracy of less than 50 percent in the diagnosis of carcinoma; but if accuracy of detection of a lesion is meant, the accuracy is very high because none of the rest of the patients developed evidence of organic disease of the stomach during the succeeding 2 or 3 years. It is interesting that Dr. Swenson detected an abnormality of the stomach which he suspected indicated malignant disease, and at operation an experienced surgeon was unable to find a lesion. A few months later the patient reappeared with an advanced lymphosarcoma of the stomach. In this instance, X-ray examination disclosed evidence of disease which escaped detection by an experienced surgeon, for the simple reason that the physical properties of the lesion were such that it could be neither seen nor felt by him.

In connection with the problem of detection of carcinoma of the stomach, I should like to mention the possibility of developing new apparatus for the amplification of fluoroscopic light with which, presumably, motion-picture films of the stomach could be made routinely. Sometimes in the course of a prolonged fluoroscopic observation a peristaltic movement may occur only once or twice. This movement may be of profound significance. Under the fluoroscope it is a fleeting thing; but if it were possible to record it on a motion-picture film and then study it at leisure, I believe that the accuracy of our judgment would be improved. Some of the manufacturers, I am quite sure, are now working or intend to work on such equipment. Possibly this group could encourage the development of that apparatus.

Miss Eleanor Macdonald (Connecticut State Department of Health): We have in Connecticut, or we shall have in 2 months, the answers to some of the questions that Dr. Ivy, Dr. Palmer, and others have asked, because we have a registry of all the admissions for cancer to all the hospitals in the State since January 1, 1935. We have followed all these cases with only about 5 percent loss. The cases of gastric cancer, of which there are 2,809 through 1945, constitute 8.5 percent of the total cases registered. That is an 11-year experience in 1 State. New patients were admitted to these hospitals for gastric cancer at the rate of 10.2 per 100,000 population per year. These figures are being analyzed now. I thought it might be interesting to know that for 1 specific section of the population, the State of Connecticut, in which approximately 1 of 3 belongs to a hospital-insurance group, we know the experience in hospitalized gastric carcinoma with regard to treatment, delay, follow-up, and survival and cure rates. Verification of every death is the practice.

Dr. Wakerlin: Mass surveys of populations for cancer would become quite feasible if we had a good serologic test for cancer; and I wonder whether any members of this conference have any published work which they would care to mention, indicating progress or difficulties along that line.

Dr. Wangensteen: Dr. Figge's suggestion of the futility of examining people over 40 years old reminds me of Benjamin Franklin's parable about Methuselah. He said that when Methuselah was 500 years old, an angel appeared and told him to build a house.

Methuselah asked, "How long am I to live?"

The angel told him, "More than four hundred years."

Methuselah said it wasn't worth the trouble.

I think Dr. Samuel Johnson said that all of us are leaking ships. It isn't a matter of who is going to survive but how long we can keep afloat.

Those of us who are dealing with the cancer problem must, of course, agree with Seneca that old age is an incurable disease. Just like an old

automobile, one part breaks down at a time. New automobiles are hard to get, and new bodies too are hard to get, so we had better keep them alive as best we can.

One of my associates just recently did a gastric-cancer operation on a fellow who was 83; he was quite garrulous and thought he was living in the town that he had left 7 or 8 years before. My associate fixed him up pretty well from a surgical point of view; but when he had done that, nobody wanted the poor fellow, and the only alternative for the surgeon appeared to be to take the patient home with him.

There is a real problem involved in this, but I suggest that until society prepares a way for us, we had better remember our Hippocratic oath and do the things we are privileged to do. If we fail to do that, we do not merit the license or the protection that a medical diploma affords us. However much we deplore the circumstances that patients with gastric cancer are near or past the Bibical three score and ten, or that for many of them only a palliative operation can be done, nevertheless, we should deal with these situations as best we can. I am agreed, however, that a greater effort should be made to have patients come for operation for gastric cancer at an earlier date; in other words, the time has come to put more emphasis on the early recognition of gastric cancer.

A number of speakers have alluded to the problem of total gastrectomy in augmenting cures in gastric cancer. That is a very important point. Dr. Pack mentioned it, and Dr. Warren likewise alluded to it. An English surgeon, Hey Groves, stressed the point of removing the great omentum; Finsterer also stressed it. I am certain that every surgeon who operates now for gastric cancer does that, but not every surgeon who operates for gastric cancer removes the gastrohepatic omentum. There are lymph nodes in it, and surgeons who profess to do a radical operation for gastric cancer must perforce remove the entire lesser curvature from the pylorus to the esophagus. Surgeons who fail to remove the entire lesser curvature in operating for gastric cancer would not do an incomplete operation like that when operating for cancer of the breast. Many years ago, Halsted defined the principle that in operating for breast cancer the axillary lymph nodes must be removed, and not the breast alone. And so, too, with the stomach.

I agree that we should do more total gastrectomies; the reason we do not is that most of us find that we can do an extensive subtotal gastric resection with less risk to our patients. Total gastrectomy for all such patients, though it would undoubtedly increase the likelihood of cures in many instances, would result in an increased early operative mortality.

And when one can do gastric resections for cancer with an operative risk of approximately 5 percent, one should not hesitate too much in a given instance whether the lesion under scrutiny is a gastric ulcer or a gastric cancer. Mind you! you radiologists have more influence in determining what is going to be done with a patient with a gastric lesion than any of the rest of us. It behooves roentgenologists, therefore, to give careful thought to their reports. If the roentgenologist, in a borderline case, fails to alert the clinician by stating frankly that the possibility of a cancer cannot be excluded, he (the roentgenologist) may unwittingly contribute to procrastination in bringing patients with gastric cancer late to operation. Dr. Rigler, in our own hospital, has long followed this policy of alerting the internist to the possibility of cancer in gastric lesions of dubious nature.

I think there is a scheme of doing total gastrectomy which permits its being done with a risk that begins to approach that of ordinary subtotal gastric resection. You remember in Dr. Pack's picture he indicated that the esophagojejunal anastomosis was made at the antimesenteric border of the jejunum. I prefer to begin the posterior row of sutures very near the mesenteric border of the jejunum. In other words, the jejunum itself may be employed to give fixation to the esophagus posteriorly. The placement of two such interrupted rows of fine silk sutures affords a secure anchorage as well as covering for the posterior portion of the anastomosis. The slit in the jejunum for the anastomosis is then made about at the antimesenteric border. This device, when combined with Lahey's maneuver of covering the anastomosis anteriorly with the reflection of the gastrohepatic omentum onto the anterior wall of the esophagus results in a complete covering of the anastomosis extending around its entire periphery. With the use of this technique, I believe that this operation can now be done with risks which begin to approximate those that experienced surgeons are encountering in performing subtotal gastrectomy.

Dr. Schiff (*University of Cincinnati*): I fear at this point even to mention the word "achlorhydria," and I for one do not believe that achlorhydria per se has anything to do with the development of cancer but that it is rather a manifestation of some disorder which may bear relationship to gastric cancer.

There are one or two points that I should like to mention. One is that it is well to remember that in pernicious anemia achlorhydria is present in 99 percent of the cases; in atrophic gastritis it is present in a much smaller percentage; and there are certain people—I think Dr. Schindler will beat me out—whose stomachs appear normal on gastro

scopic examination and who have achlorhydria. I think if we could get a series of patients with achlorhydria and a normal stomach, achlorhydria with atrophic gastritis, and achlorhydria with pernicious anemia, and then follow the technique used in Dr. Wangensteen's clinic, we might learn more about the relationship of achlorhydria and gastritis to gastric cancer. I followed a small number of such cases through a period of 8 years and none of them have developed a gastric carcinoma. But I think the group is entirely too small, and that it is much better to work, as Dr. Wangensteen is working, with much larger groups.

I believe that in general hospitals it is not too difficult to do routine gastric analysis on patients of a certain age group and gastroscope those who have achlorhydria and follow them for a long period. Some prospects are lost; but on the other hand, we have had patients with us for a number of years, and we have gastroscoped some of them as many as 30 to 40 times, and I think Dr. Schindler has gastroscoped some patients even more than we have.

I think it would be of interest to follow patients with apparently normal stomachs and achlorhydria and see what happens to them in contrast with the other patients. That might give some information along the lines that Dr. Warren suggested, of a relationship of apparent irritation or disease to the development of carcinoma.

Chairman Spencer: Dr. Ivy, will you close the discussion?

Dr. Ivy: I believe everyone here will agree that the major emphasis should be placed on research, both experimental or fundamental research and clinical research. However, as I view our present information on the subject of gastric cancer, I believe our greatest hope lies in the discovery of some substance or means for liquefying and markedly reducing the growth of the cancer. On the other hand, I feel that it is our duty to give some attention to the matter of earlier detection of gastric cancer, and I should like to know the sense of this conference or group regarding this question. Should studies be encouraged which are designed to improve the present case-finding methods for detecting gastric cancer early?

All those who believe that the answer to that question should be yes, hold up your hands.

All those opposed, hold up your hands.

I judge that it is the unanimous opinion of this conference that studies should be encouraged which are designed to improve the present case-finding methods for detecting cancer earlier; and, of course, it goes without saying, unless I hear some objection, that the major emphasis in this over-all attack on cancer should be placed on research.

Dr. Eugene Pendergrass (Philadelphia): Dr. Ivy, will you answer the question that was asked, whether there is any serologic test being attempted to make an early diagnosis of cancer?

Dr. Ivy: So far as I know, the only serologic test which has been suggested recently for the diagnosis of cancer is the test of Dr. Gruskin.

Dr. Schiff: To your knowledge, has anything been done recently with gastric juice in an effort to diagnose gastric cancer early? Have there been any chemical studies attempted along new lines to see whether some substance might be present in the gastric juice of patients with gastric cancer that is not present in the gastric juice of others? Do you know anything about that?

Dr. Ivy: Nothing since Dr. Brunschwig reported his work on the gastric inhibitory factor of the gastric secretion. Do you agree, Dr. Barrett?

Dr. Barrett: There are some very loose observations that perhaps would add something to the points under discussion. In regard to gastric juice, there is a method, which did not impress me upon reading the literature, for finding the rate of decolorization of methylene blue in the gastric juice. The chap introduced a very small amount of methylene blue. As I remember, he used two or three drops of a 10-percent water solution of methylene blue, in about 250 or 300 cc. of fluid, which he introduced into the stomach by a tube. He then took fractional analyses, and he reports that the fractional samples taken from the stomach do show a selective decolorization, which indicates cancer. The most amazing thing about the report to me was that he somehow, with just 250 cc. of fluid in the stomach, found methylene blue there after 24 hours. I can't quite imagine what the pylorus was doing during all this time.

In regard to the serologic question, before the war (and this work was interrupted by the war), I was very much interested in this aspect, and Dr. Maver at the National Cancer Institute was preparing a pure cathepsin from hepatoma cells and from normal liver cells. It occurred to us that since this was protein in nature and since it was one of the vital enzymes of the cell, perhaps it might offer as good a point as any other at which to start investigating the serologic, or perhaps we had better say, the immunologic qualities of this intracellular substance.

This work is not completed, and I hesitate to mention it for that reason. But we did find that one could take the apparently pure cathepsin from a rat hepatoma and an indistinguishable cathepsin, that is, indistinguishable chemically, from normal cells, and if one tried them by inoculations into the guinea pig, there was a marked difference between those two cathepsins. There were some very poor

and equivocal indications that other serologic methods might also demonstrate a difference in this material. I toss that out as merely being one indication that the finding of a serologic method, which I am sure most of the people in the room feel is quite hopeless—and I almost feel that way myself—may not be altogether hopeless.

There is one other thing in regard to gastric tissue, and again I just toss this out as something that is in the literature. I couldn't quite swallow it. There is a group of workers from Rumania who report that biopsy of gastric tissues shows that the topographic distribution of vitamin C in these tissues differs between normal and pathologic stomachs, and they even go to the extent of drawing a diagram of the concentration of vitamin C in relation to its anatomic position in the stomach. They found one very high level at a slight distance from a cancer. The paper is in French, and the word they used was that this point was the "zone de barrage." Just what they mean by that, you are as able to interpret as I am. They did say, however, that this point was the site of the next metastasis.

So there are some little things in the gastric juice itself that some people think might be important.

Dr. Ivy: According to my knowledge, if methylene blue is present in the stomach in significant amounts 24 hours after administration, there must have been some gastric retention. Referring to cellular chemistry, I believe that much valuable information may be derived from a study of the chemistry of mucins. There are different forms of mucin secreted by the gastric mucosa. It is possible that the early cancer cell may produce a specific type of mucin, or a mucin different from that produced by the adult mucin-secreting cell.

Chairman Spencer: Thank you, Dr. Ivy. Before we adjourn, Dr. Cowdry has a motion to put before the group.

Dr. Cowdry: This is a motion that carries unanimously. It is that the conference extend thanks to Dr. Brunschwig and to the University of Chicago for their hospitality, which has made this conference so very instructive and enjoyable. (Applause.)

The meeting adjourned at 12:30.

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ATTENTION is invited to the Fourth International Cancer Research Congress to be held in St. Louis, Mo., September 2–7, 1947.